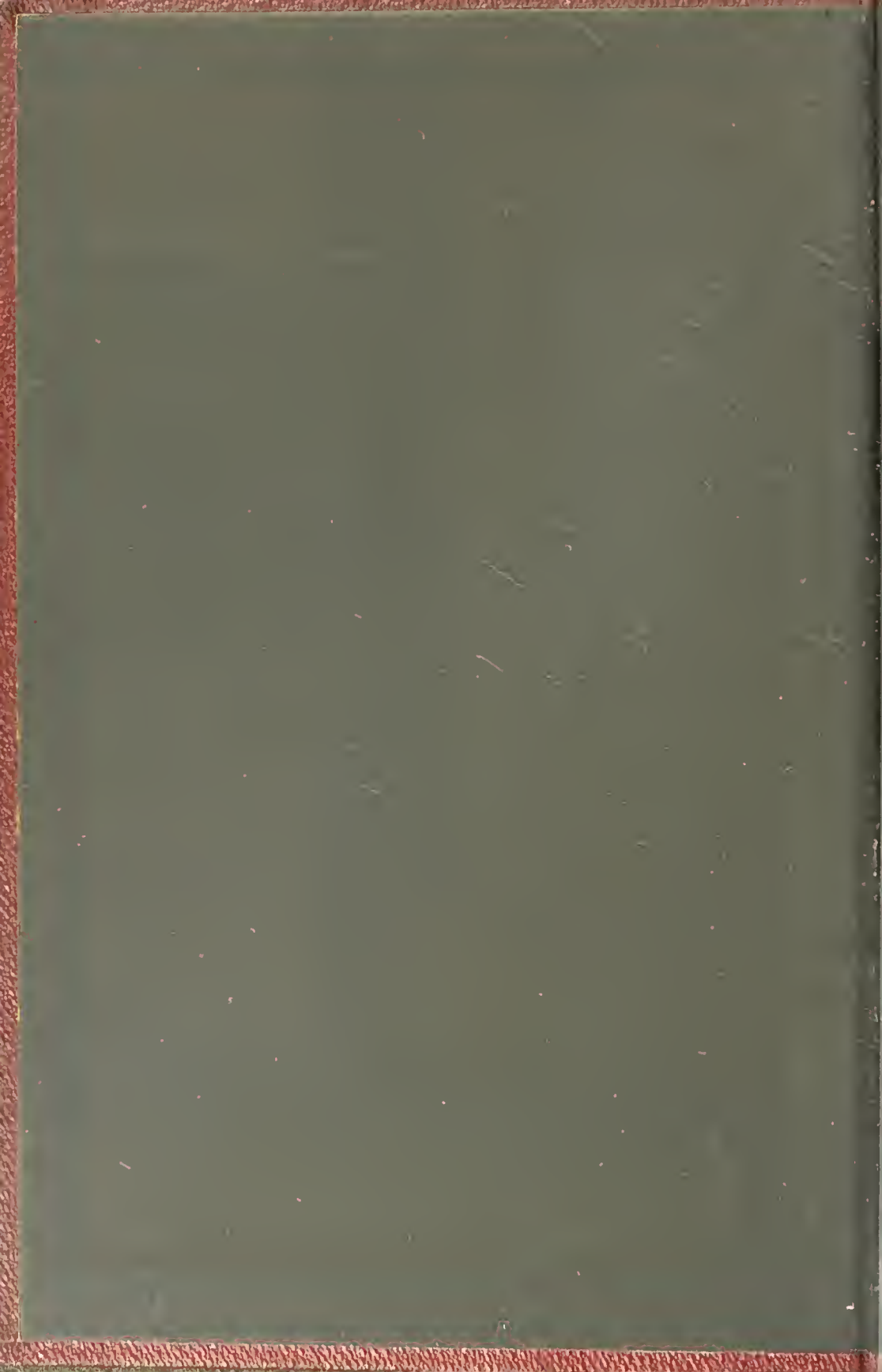


URINE

AND URINARY ANALYSIS

CAMPBELL BLACK





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THE URINE IN HEALTH AND DISEASE, AND
URINARY ANALYSIS.



THE
URINE IN HEALTH AND DISEASE,
AND
URINARY ANALYSIS

*PHYSIOLOGICALLY AND PATHOLOGICALLY
CONSIDERED.*

BY

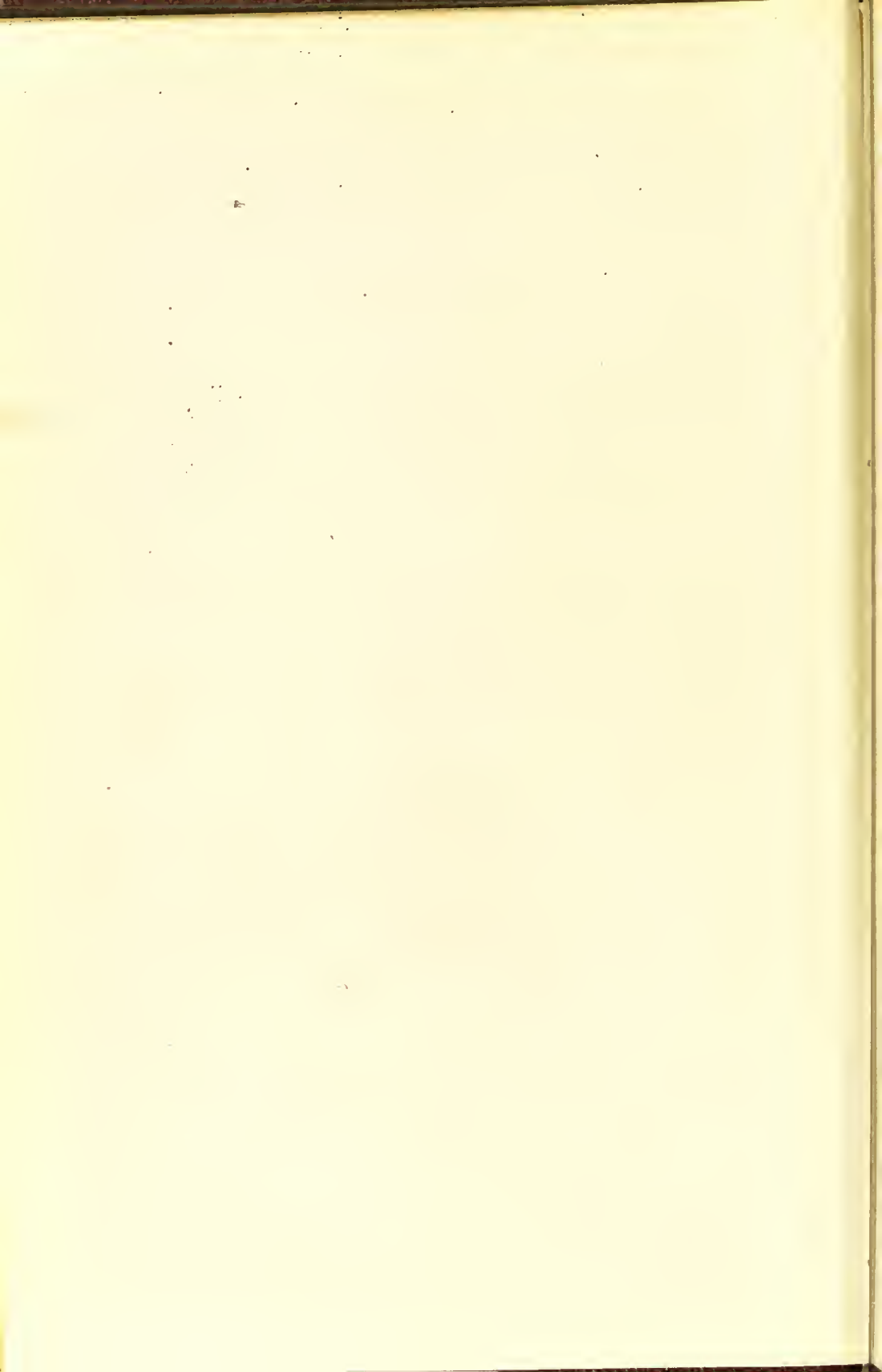
D. CAMPBELL BLACK, M.D., L.R.C.S. EDIN.,
F.F.P. & S. GLAS.,

PROFESSOR OF PHYSIOLOGY IN ANDERSON'S COLLEGE MEDICAL SCHOOL; PHYSICIAN
TO THE GLASGOW PUBLIC DISPENSARY (DEPARTMENT FOR KIDNEY AND
URINARY DISEASES); FORMERLY SENIOR ASSISTANT-PHYSICIAN
TO THE GLASGOW ROYAL INFIRMARY, ETC., ETC.



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PREFACE.

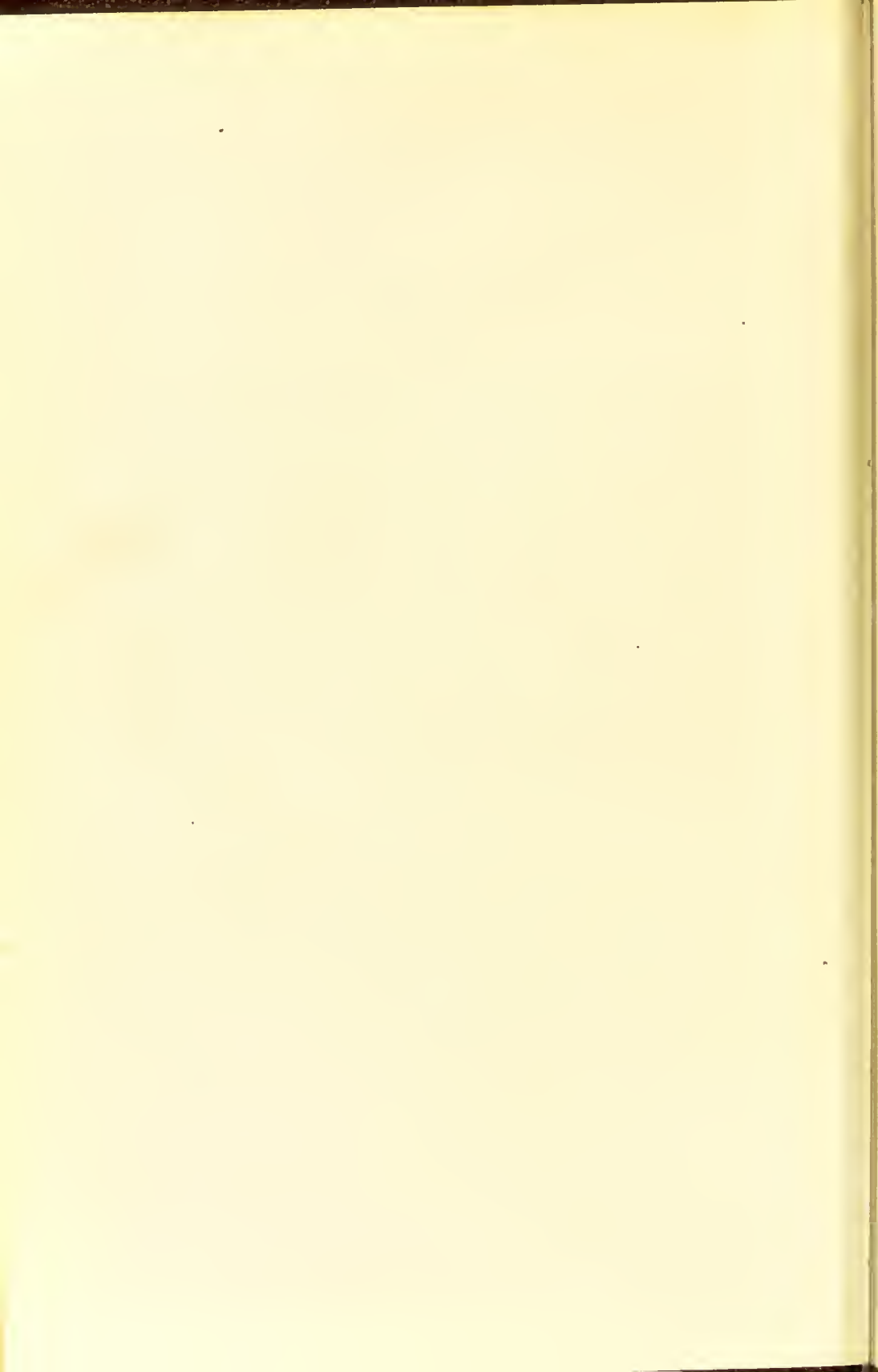
A LARGE experience of medical students has impressed me with the conviction that the importance which they attach to the examination of the urine, so important in throwing light on many obscure phenomena of disease, is usually not such as the subject merits. Nor are students altogether to blame; they are rather to be sympathized with in the enormous amount of details, many of them totally irrelevant to the scientific practice of medicine and surgery, which are embraced in the short curriculum of study at their disposal, and which consequently render an accurate knowledge of them absolutely impossible. Within recent years the department of urology has so developed as almost to constitute a distinct science. Many of its minutiae are devoid of practical bearing, and many of the constituents described as existing in the urine, not a few of which I believe to be manufactured in the so-called process of isolation, may be regarded as the curiosities of the chemist's laboratory. In the following pages I have aimed at conciseness and the treatment of the subject from the practical and clinical standpoint.

I have endeavoured to incorporate the latest useful information, and I hope that the book may prove acceptable to such as are fully occupied in practice, and are without ready access to the extensive current and other literature of the subject.

To my friend and colleague, Professor Robertson Watson, I acknowledge my cordial obligations for his invaluable services in supervising the greater portion of the proofs.

D. C. B.

GLASGOW, *October*, 1894.



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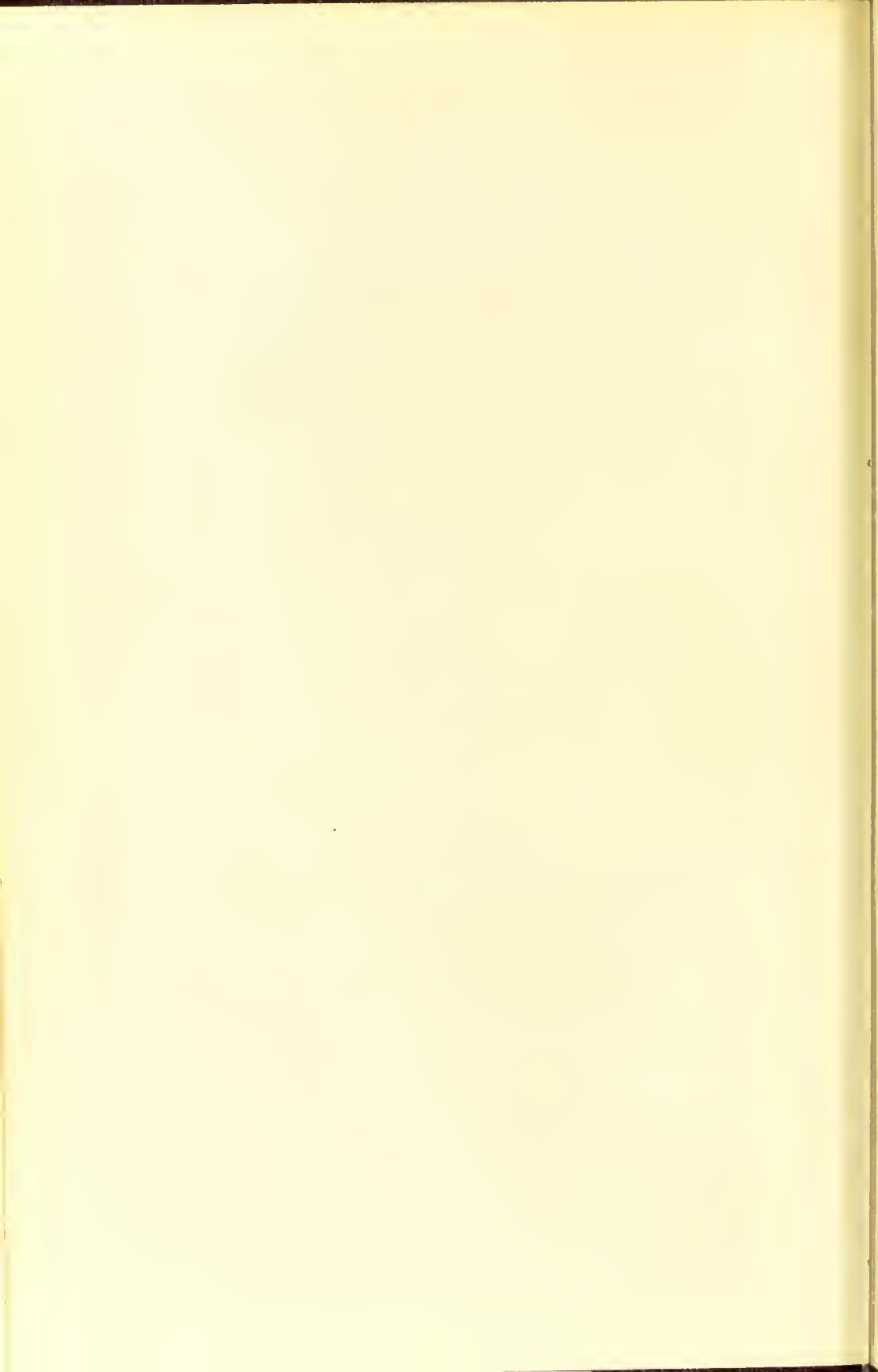
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THE
URINE IN HEALTH AND DISEASE
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URINARY ANALYSIS

PART I.

CHAPTER I.

ANATOMY AND PHYSIOLOGY OF THE KIDNEY.

Semeiology—Size of the Kidney—Weight of the Kidney—Basement Membrane or Stroma of the Kidney—The Malpighian Capsule—The Glomerulus—Circulation of Blood in the Kidney—The Renal Vein—Lymphatics of the Kidney—Nerves of the Kidney—Theories of Secretion of Urine—Relation between Urinary Secretion and Arterial Pressure—Transparency of Urine—Odour, Colour, Fluorescence, Temperature, Quantity of Urine—Hydruria and Polyuria—Influence of Pathological States—Variation of Density and Solid Residue in Disease—Specific Gravity of Urine—Density of Urine—Estimation of Total Solids—Reaction of Normal Urine—Determination of the Degree of Acidity—Alkalinity of Urine—Variations in Reaction of Urine—Chemical Composition of the Urine—Toxicity of the Urine—Pathological Sediments and Concretions—Accidental Elements of the Urine—Reactions of Normal Urine and Significance.

By the department of medicine termed semeiology (σημείον, a sign) is understood that which treats of the signs of disease as illustrating and explaining the nature of the departure from health with which these signs are associated, and of which they are the evidences. In this there is of necessity implied a knowledge of the healthy functions and a valid process of deductive

reasoning. The functions of the kidney, and the significance attached to the modifications and varieties of its secretion and excretion as bearing upon disease and indicating rational treatment, have engaged attention from the birth of medicine as a science. Two organs, placed in the abdominal cavity, but outside the peritoneum, the kidneys are situated on either side of the vertebral column in the lumbar region. The right kidney is usually placed at a lower level than the left. The appearance of the kidney is so characteristic that the term reniform is usually employed to describe it and bodies of a similar form. It has not inaptly been compared in outline to that of a haricot-bean, the *hilus*, or depression, through which the ureter, the blood-vessels and nerves enter being directed towards the spine.

As a rule, the two kidneys are identical in size; but occasionally differences in size are encountered as abnormalities quite compatible with health. In certain rare instances but one kidney exists, this abnormality arising from an intra-uterine coalescence of the two primitive glands.

The Size of the Kidney varies with age, sex and general development of the individual. Ordinarily the kidneys measure about 4 inches in length, $2\frac{1}{2}$ inches in breadth, and $1\frac{1}{4}$ inches or more in thickness. The left kidney is sometimes the longer and thinner, the right being shorter and wider.

The Weight of the Kidney likewise varies with age and development. In the adult male it usually weighs about $4\frac{1}{2}$ ounces, being somewhat less in the female. According to Glendinning, the two kidneys of the male weigh on an average $9\frac{1}{2}$ ounces, and those of the female 9 ounces. According to the observations of Reid, the average weights of the kidneys are, in 160 observations by him, $4\frac{1}{2}$ to 6 ounces in the adult male, and in the adult female (74 observations) 4 to $5\frac{1}{2}$ ounces. The specific gravity of the renal substance is 1052. The superficial colour of the kidney is a deep reddish-brown.

Chemically the kidney contains 83 per cent. of water, 1 per cent. of fatty matter, and the 16 remaining constituents almost exclusively represent albuminoid compounds.

Like all other glands, the kidney may be structurally regarded as composed of a basement membrane or matrix; a series of tubes

for depuratory purposes communicating directly or indirectly with the exterior; a system of cells for separating and elaborating the ultimate products of waste; a system of blood-vessels supplying nourishment to the organ and conveying to it the products to be secreted and excreted; and a system of nerves regulating the circulation of the blood. Independently of these, the kidney possesses a lymphatic system. The functions performed by the kidney in the aggregate are simply those performed by the single cell, and may be classified as physical, vital, and chemical; the physical consisting of dialysis and taking place in the glomerulus and Malpighian capsule; the vital in the special selection manifested by the glandular structure in the discharge of the function of excretion; and the chemical in the elaboration and the separation of the ultimate products of oxidation in the body.

The Basement Membrane or Stroma of the Kidney.—Externally the kidney is invested by a thin and strong fibrous coat, the *tunica propria*, which is loosely attached to its substance by a delicate areolar tissue and minute bloodvessels. Prolongations from the *tunica propria* extend inwards in the tissue of the organ, and are continuous with the connective tissue proper presently to be noticed. When the *tunica propria* is traced to the *hilus*, it is found to be continuous with the external surface of the infundibulum formed by the dilated portion of the emergent ureter, and the adherent nutrient bloodvessels which enter at this part. On making a section of the kidney from its outer to its inner border the fissure, or *hilus*, is found to extend some distance into the organ, forming a cavity termed the sinus, into the bottom of which the fibrous coat can be traced. The emergent ureter is greatly enlarged before it leaves the organ by the union of its primary subdivisions forming a chamber termed the pelvis. Into the substance of the organ prolongations of the ureter pass which terminate abruptly in cup-like depressions called the calyces, into which little conical protrusions depend—the Malpighian pyramids. The outer capsule of the kidney consists of connective tissue chiefly of the white fibrous variety, which, on being examined with a high power, is found to contain flattened connective tissue corpuscles. This tissue is most compactly arranged towards the periphery.

becoming areolar in its deeper portion, the tenuity of its fibres increasing as it dips down and becomes continuous with the intertubular tissue of the subjacent cortex. Between the cortex and the capsule there is a system of bloodvessels and elongated cells, described by Eberth as a plexus of non-striated muscular fibres.

The existence of connective tissue in the kidney, long disputed, was first maintained by Goodsir. This view was afterwards combated by Von Wittich, who maintained that the interstices of the secretory and excretory portions of the kidney were merely separated by capillary vessels. This opinion held ground, especially among German histologists, until Arnold Beer published the results of his investigations.* The connective tissue in the normal state is found in greatest abundance at the level of the hilus, and is distributed along the bloodvessels, and serves to support them in the same manner as that of the liver. As the connective tissue is traced inwards from the papillæ it becomes less manifest. It contains cell elements, fibres, and, according to Ludwig, lacunar spaces in connection with the lymphatic system. Processes of the connective tissue, as we have seen, dip inwards from the capsule into the cortical substance, and, like the connective tissue in other glands, these enlarge on the supervention of interstitial change, and undergo contraction and other morbid changes, thus destroying the glandular tissue and abrogating its proper function, the whole process being the sequence of initial hyperæmia abnormally protracted. This multiplication and change of connective tissue is an important factor in a large class of diseases, not only in the kidney, but in the lungs, liver, and spinal-cord, etc. (cirrhosis). It is in it that abscesses form, and that the great bulk of neoplasms are developed. Axel Key first noticed that connective tissue exists in the glomerulus, binding together the capillary loops, and becoming continuous with the tissue which surrounds the afferent arterioles, and the medullary substance of which they are branches. From there the tissue may be traced round the arteriole rectæ into the boundary layer between the medulla and the cortex, when it

* 'On the Connective Tissue of the Human Kidney in its Physiological and Pathological Relations,' 1859.

becomes scanty and assumes a hyaline, honeycombed, membranous aspect. According to Schweigger-Seidel, in this situation the connective tissue may be branched or spindle-shaped and possess oval nuclei disposed transversely to the long axis of the tubules. On macroscopic (*μακρός*, great) examination a section of the kidney shows certain clearly-defined differentiation of structure. Fundamentally, the gland is seen to be composed of an external or cortical portion, and a medullary portion directed from the cortex towards the hilus. The cortical portion occupies the entire surface of the organ, is of a dark-brown chestnut colour, and forms a layer of about two lines in thickness. It is friable, easily lacerated, and when this does take place the laceration usually happens in a direction vertical to the surface. The rupture presents an irregular appearance due to an admixture of straight and convoluted tubes and Malpighian bodies.

From the cortical substance, and passing towards the hilus, prolongations are sent, which separate and form partitions between the pyramids of Malpighi. These septa terminate near the summit of the papilla, and are known as the columns of Bertini (*septula renum*). It is in the cortical substance and its prolongations that morbid changes are most frequently found.

Between the *septula renum* another collection of tubes is seen, constituting the pyramids of Malpighi, the bases of which are directed towards the cortex of the organ, and their apices towards the hilus, terminating in the papillæ which open into the calyces. The number of these pyramids varies from eight to eighteen. In ultimate structure these pyramids are composed of a series of straight tubes (tubes of Bellini) placed parallel to the axis of the pyramid, and presenting a striated aspect. Passing towards the cortex, these tubes divide and subdivide at very acute angles. At the base of the pyramids of Malpighi they unite with the convoluted tubes; and it is this union of the collector with a convoluted tube which constitutes a pyramid of Ferrein.

The Malpighian Capsule.—By the Malpighian capsule, or capsule of Bowman, is understood the dilated cortical extremity of the uriniferous tubule, whose other extremity terminates in

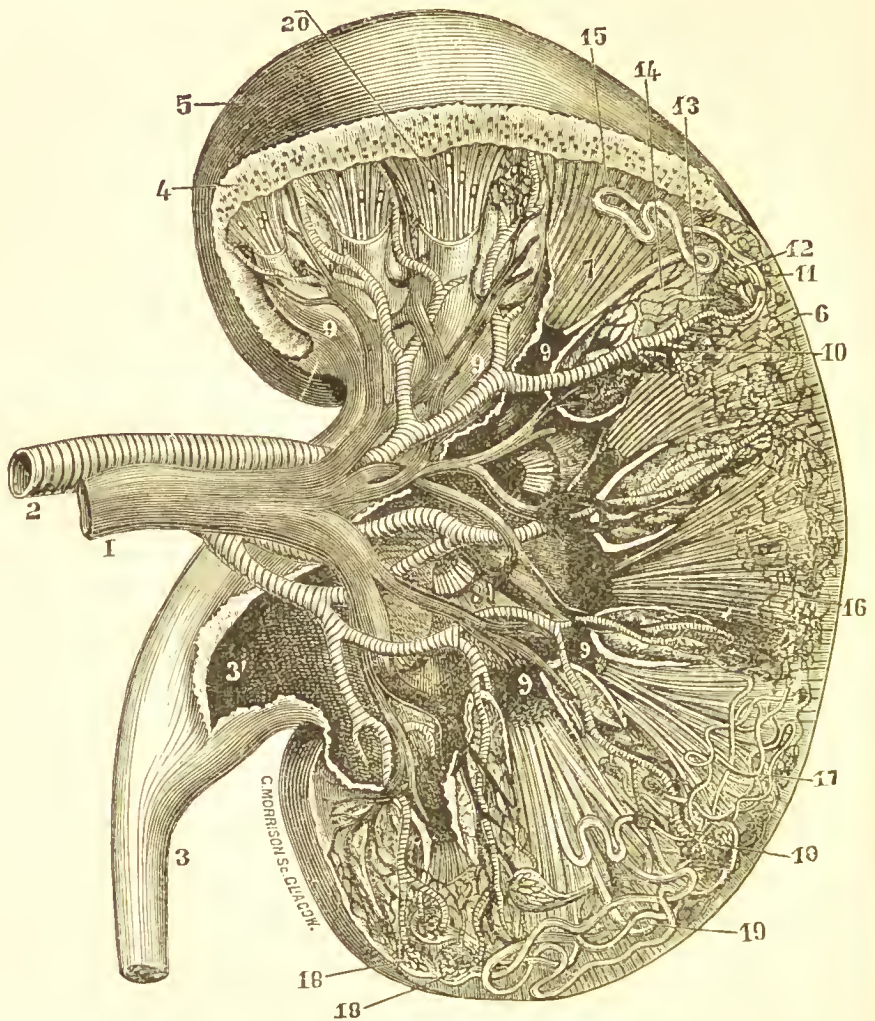


FIG. 1.--GENERAL VIEW OF THE STRUCTURE OF THE KIDNEY (the tubes of Henle not represented).

1, Renal vein ; 2, Renal artery ; 3, Ureter, continuous with the open pelvis ; 4, Cut cortex of the kidney ; 5, Surface of the kidney ; 6, Cortical substance ; 7, A Malpighian pyramid with its arteries : 8 8, Papillæ of pyramids which have not been divided ; 9, A divided calyx, embracing a pyramid ; 10, Branch of the renal artery between two pyramids ; 11, Malpighian capsule magnified 40 diameters ; 12, Vessels in the centre of the glomerulus ; 13 Efferent vessel of the glomerulus : 14, Capillary network ; 15, Convolted tube of the cortical substance $\times 20$; 16, Tortuosities of convolted tube ; 17, Tortuous tubes $\times 40$; 18 18 18, Glomeruli $\times 10 \times 20$; 19, Tortuous tubes $\times 20$ to 25 ; 20, Some tubes cut.

the papilla. It embraces within its walls a tuft or network of bloodvessels, termed the glomerulus, from which vessels the urine, with certain of its diffusible salts, is secreted. In structure the capsule consists of a hyaline *membrana propria*, thickened, according to Ludwig, externally by a greater or less proportion of a delicate fibrous tissue dipping inwards to form an investment for the glomerulus. The inner surface of the capsule is lined by a layer of epithelial cells. These cells undergo certain physical changes, according to age. In early life they are somewhat polyhedral in form, while as age advances they become flattened. They all possess well-marked oval nuclei, which may be distinctly revealed by injecting the renal bloodvessels with a solution of nitrate of silver. In like manner the glomerulus is covered with its own special epithelial cells, which are considerably larger than those lining the capsule, and remain of

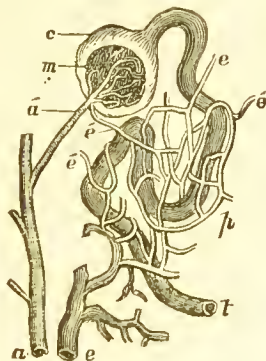


FIG. 2.—DIAGRAM SHOWING THE RELATION OF THE MALPIGHIAN BODY TO THE URINIFEROUS DUCTS AND BLOODVESSELS. (*After Bowman.*)

a, One of the interlobular arteries; *a'*, Afferent artery passing into the glomerulus; *m*, Vascular tuft formed within the glomerulus; *c*, Capsule of the Malpighian body (capsule of Bowman) forming the termination of and continuous with *t*, the uriniferous tube; *e*, *e'*, Efferent vessels which subdivide into the plexus *p*, surrounding the tube, and finally terminate in a branch of the renal vein *v*.

a polygonal shape (cubical). These two epithelial layers constitute thus a closed sac, containing an excreting gland.

The Glomerulus.—The glomerulus is a tuft of bloodvessels composed of terminal branches of the renal artery and the

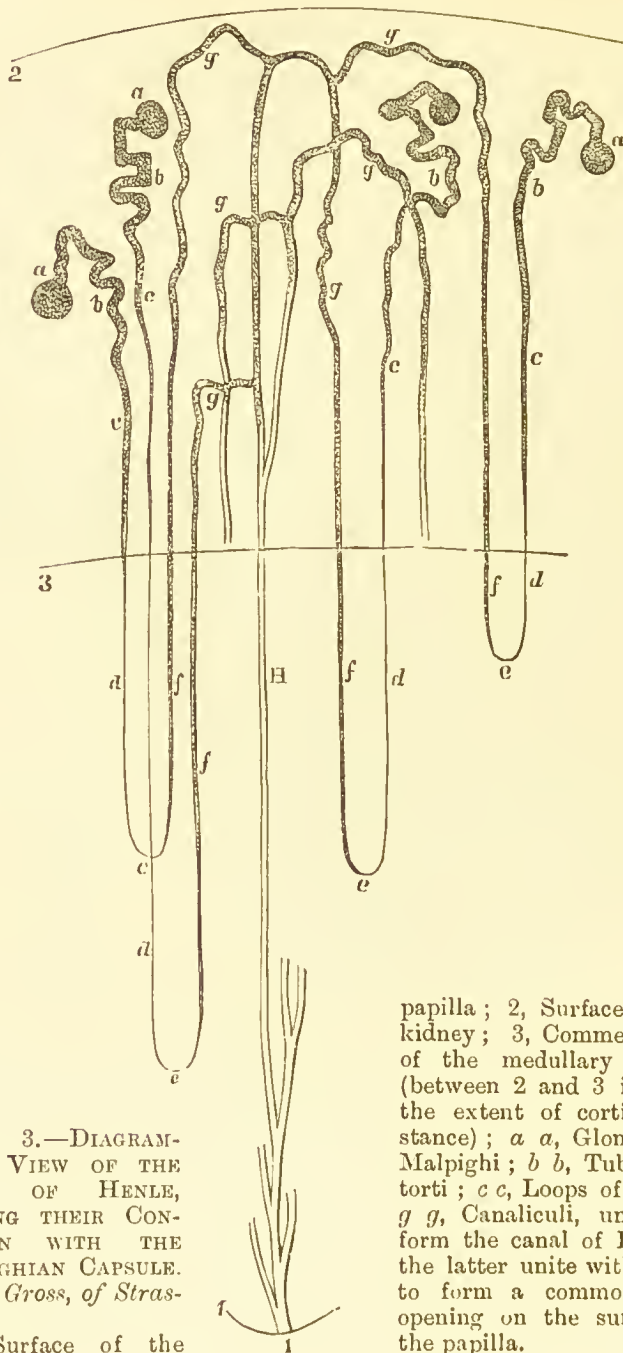


FIG. 3.—DIAGRAM-
MATIC VIEW OF THE
LOOPS OF HENLE,
SHOWING THEIR CON-
NECTION WITH THE
MALPIGHIAN CAPSULE.
(After Gross, of Stras-
burg.)

1, Surface of the

papilla; 2, Surface of the
kidney; 3, Commencement
of the medullary portion
(between 2 and 3 indicates
the extent of cortical sub-
stance); *a a*, Glomeruli of
Malpighi; *b b*, Tubuli con-
torti; *c c*, Loops of Henle;
g g, Canaliculi, uniting to
form the canal of Bellini—the
latter unite with others to
form a common canal
opening on the summit of
the papilla.

commencing branches of the venous system. On reaching the Malpighian capsule, the afferent artery pierces its homogeneous envelope and breaks up into smaller tortuous branches, which ultimately unite to form an efferent vein, which makes its exit from the capsule near the entrance of the artery, and unites with the intertubular venous plexus surmounting the convoluted tubes, all of which ultimately join the renal vein.

At a point opposite to the entrance of the afferent artery and the exit of the efferent vein, the glomerulus becomes continuous with the canal of the convoluted tube. At the point of junction the canal is narrowed, and to this portion the term 'neck of the capsule' has been applied. Commencing at this neck, the canal, situated in the cortical substance, becomes tortuous, of considerable size, and is now designated the convoluted tube, in virtue of its appearance. After a short course as a convoluted tube, termed the proximal convoluted tubule, the canal becomes narrowed, and descends in the form of a straight tube towards the papilla. This portion is termed the descending branch, or the small branch of the loop of Henle. Within a variable distance of the papilla the canal abruptly bends upon itself, forming an ascending branch, or great branch of the loop of Henle, which runs parallel with the smaller one, and again narrows into a spiral portion, then dilates into a tortuous tube, forming the distal convoluted tubule, which opens into a collecting or straight tubule. It is the junction of the distal convoluted tubule with the straight tubule which constitutes the pyramid of Ferrein. The distal convoluted tubule is also known as the intercalated portion (*Schalstück*, Schweigger-Seidel).

As function is specialized in certain portions of the kidney, we accordingly find that the cells lining the secreting tubes differ correspondingly. (1) In the proximal convoluted tubule there is a single layer of epithelial cells, which reduces its lumen to about a third of its whole diameter. In general outline the cells of this section are somewhat cubical; towards the neck they decrease very markedly in height, and have thus the appearance of ceasing abruptly there. They vary in size throughout the tubule, and their opposed sides are not straight, but slightly

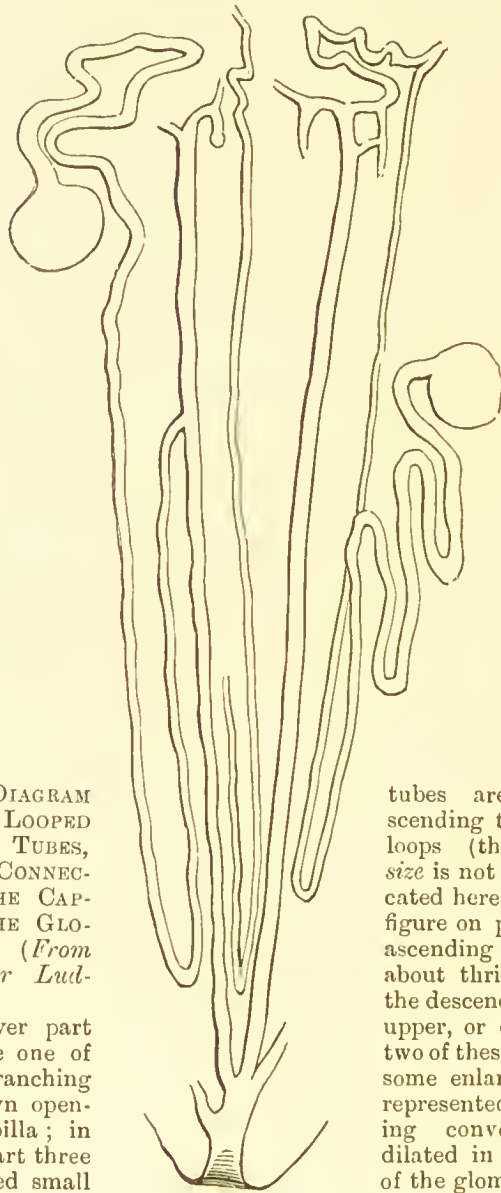


FIG. 4.—DIAGRAM OF THE LOOPED URINIFEROUS TUBES, AND THEIR CONNECTION WITH THE CAPSULES OF THE GLOMERULI. (*From Southey, after Ludwig.*)

In the lower part of the figure one of the larger branching tubes is shown opening on a papilla; in the middle part three of the looped small

tubes are seen descending to form their loops (their *relative size* is not so well indicated here as in Gross's figure on page 8. The ascending branch is about thrice the size of the descending). In the upper, or cortical part, two of these tubes, after some enlargement, are represented as becoming convoluted, and dilated in the capsules of the glomeruli.

curved, the convexity of the one side fitting into the concavity of that in juxtaposition with it. All the cells possess central spherical

nuclei. Klein describes the structure of these cells as consisting of a honeycombed network. (2) In the spiral tubule of Schachowa, the relative size, shape of the walls, and lumen resemble the proximal convoluted tubule. The cells at the commencement of this section are very irregular in shape, some of them being elongated columnar cells with concave sides, while others are broad with convex sides and convex free surfaces, thus resembling mushrooms, and called the fungoid cells of Schachowa. They all possess centrally-situated spherical nuclei. (3) In the descending limb of Henle's loop the epithelial cells become attenuated, and contain oval, flattened, centrally-placed nuclei. (4) In the ascending limb of the loop of Henle the epithelial cells become modified into polyhedral forms with a based rod-like striation. Each cell possesses a strongly-marked spherical nucleus, situated towards the free extremity, which projects into the lumen. (5) In the spiral portion of the ascending limb of Henle's loop the epithelial cells contain oval, irregular, and flattened nuclei placed towards the lumen, which is almost obliterated by the large size of the polyhedral striated cells. (6) In the cortical portion of the ascending limb of Henle's loop the cells show rod-like structure at their attached bases, and possess flattened or angular peripheral nuclei, occasionally with imbricated processes. (7) In the irregular tubule the epithelial cells are imbricated, and exhibit the rod-like structure more markedly than in any other portion of the renal tube. Each cell contains an oval or angular nucleus towards its periphery. (8) The intercalated section is identical in location and structure with the proximal convoluted tubule. (9) The straight section of the collecting-tube has a small but distinct lumen with a single layer of homogeneous cells, varying in shape from regular polyhedral to flattened or spindle-shaped elements. The cells possess ovoid or spherical nuclei, and may show imbricated processes. (10) The collecting-tube of the boundary layer is lined with epithelial cells of a short columnar variety, resembling those of the foregoing portions. (11) In the collecting-tubes and ducts of the papillary portion the size of the lumen and its epithelial cells depends on the diameter of the tube, which increases by the successive

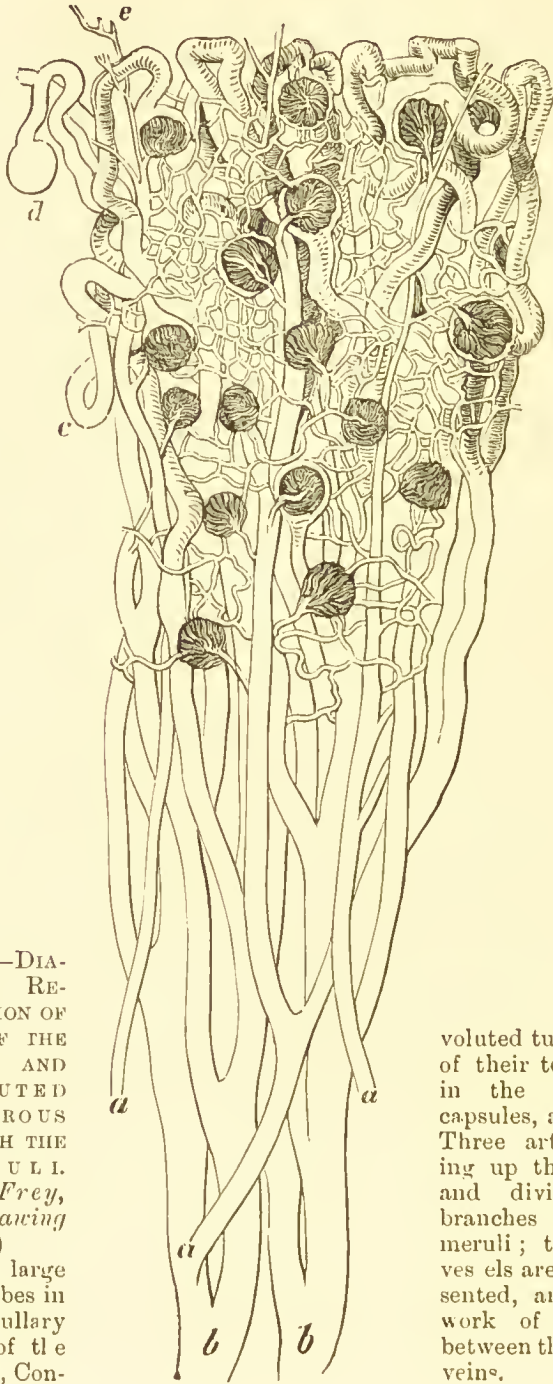


FIG. 5.—DIA-
GRAMMATIC RE-
PRESENTATION OF
A PART OF THE
STRAIGHT AND
CONVOLUTED
URINIFEROUS
TUBES WITH THE
GLOMERULI.
(From Frey,
after a drawing
by Müller.)

b b, Two large
straight tubes in
the medullary
substance of the
pyramid; *c*, Con-

voluted tubes, several
of their terminations
in the Malpighian
capsules, as in *d*; *a*,
Three arteries pass-
ing up the pyramid,
and dividing into
branches to the glo-
meruli; the efferent
vessels are also repre-
sented, and the net-
work of capillaries
between them and the
veins.

union of smaller ducts, until it forms the large duct of Bellini, which debouches on the papilla.

Circulation of Blood in the Kidney.—The kidneys are abundantly supplied with blood through the renal arteries, which branch off from the aorta between the two mesenteric arteries. Each is directed outwards so as to form nearly a right angle with the aorta. Owing to the position of the aorta on the spine, the right renal artery, in order to reach the kidney, has a longer course than the left, and it runs behind the vena cava. Both arteries are covered by the renal veins. Relatively to the size of the kidney the renal artery is large, and the organ is thus highly vascular. On reaching the hilus the renal artery enters the organ between the renal vein and the ureter, and usually divides into four or five primary branches, which may be seen in the sinus to pass in amongst the infundibula. These branches are usually surrounded by a large proportion of adipose tissue. The arteries now further divide and subdivide to enter between the Malpighian pyramids, that is to say, in the substance of the columns of Bertini. They are surrounded by longitudinal and circular bands of muscular fibres, and by a delicate connective tissue, which accompanies them in their course throughout the papillary region. A little before reaching the base of the pyramid they divide and anastomose between one another, the intercommunicating arterial network forming an arterial incomplete arch, whose convexity is towards the surface of the kidney. By its concavity this arch gives branches to the pyramids, and by its convexity it furnishes numerous branches proceeding perpendicularly towards the cortical substance. In the course of these branches short, transverse off-shoots are distributed (in the cortical substance), one to each Malpighian capsule forming its afferent artery, and breaking up in the loop, forms terminal branches anastomosing with the efferent vein. Occasionally the afferent arterioles give off lateral branches before they reach the glomerulus, which ramify around the convoluted tubules. In the portion of the cortical substance which is devoid of Malpighian capsules, the interlobular arteries either terminate as afferent arterioles, or continue towards the capsule, supplying the network of capillaries surrounding the convoluted tubes, or

anastomose with branches from the lumbar artery, with which the capsule is thus supplied. It is thus obvious that the kidney has a blood-supply independently of the renal artery; and thus, if the renal artery be tied, the kidney may be injected through the aorta by means of these lumbar branches. From the larger

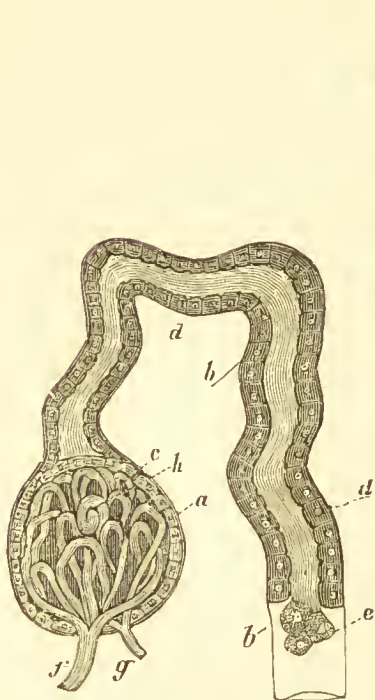


FIG. 6. SEMIDIAGRAMMATIC REPRESENTATION OF A MALPIGHIAN BODY IN ITS RELATION TO THE URINIFEROUS TUBE. (From Kölliker.)

a, Capsule of the Malpighian body continuous with *b*, the *membrana propria* of the coiled uriniferous tube; *c*, Epithelium of the Malpighian body; *d*, Epithelium of the uriniferous tube; *e*, Detached epithelium; *f*, Afferent vessel; *g*, Efferent vessel; *h*, Convoluted vessels of the glomerulus.



FIG. 7.—THREE MALPIGHIAN CAPSULES IN CONNECTION WITH THE BLOODVESSELS AND THE URINARY TUBES OF THE HUMAN KIDNEY. (From Kölliker, after Bowman.)

a, Termination of an intertubular artery; *b*, Afferent arteries; *c*, A denuded vascular glomerulus; *d*, Efferent vessel; *e*, Two of the glomeruli enclosed by the Malpighian capsules; *f*, Uriniferous tubes connected with them.

arterial branches existing between the cortex and the medullary structure another system of branches arises. Those entering the boundary layer proceed towards the papilla in groups parallel with and between the renal tubules. These are the *arteriolar rectæ*, which impart the peculiar banded appearance to the medullary rays. As they approach the papilla they decrease in number owing to the lateral branches which they give off, and around the mouths of the ducts they terminate in a network of capillaries continuous with the *venæ rectæ*, which pursue an opposite direction directly parallel.

The Renal Vein originates in the efferent vessel of the glomerulus and the capillary venous system of the kidney generally. The efferent vessel, as we have seen, considerably smaller than the afferent, originates in the Malpighian tuft. Penetrating in its outward passage the Malpighian capsule near the entrance of the afferent vessel, it breaks up into a dense network of veins, which surround the convoluted tubes and closely embrace them. The meshes of the labyrinth and periphery are smaller and more regular in disposition than those in the medullary structure, which become more elongated. The capillaries of the periphery of the cortex open into minute veinlets, which again empty into larger vessels forming rays, and hence termed *venæ stellatæ*. The *venæ stellatæ* become interlobular veins, and accompanying the interlobular artery between the cortex and the medulla, form a venous arch, in which the *venæ rectæ*, commencing in the papilla, terminate.

The blood in the efferent vein of the glomerulus is still red, and hence this vessel is sometimes termed an artery. The specific urinary constituents, such as urea, hippuric acid, etc., are not separated from it until it reaches the convoluted tubes. Unlike all the other venous blood of the body, it is not surcharged with carbonic acid gas. That of the body in general contains 6 per cent. of oxygen, while that of the renal vein contains 16 per cent., or only 1 per cent. less than that of arterial blood.

Lymphatics of the Kidney.—According to Sappey, the kidney possesses no superficial lymphatics, while the origin of the deep lymphatics is as yet undetermined. They are in free communication with the lymph spaces which surround the con-

volute tubes of the cortex. A plexus of lymphatic vessels exists around the larger bloodvessels which enter the medulla; and, according to Ludwig and Zawarzkín, a system of intertubular lymph spaces communicates freely with a superficial capsular system.

Nerves of the Kidney.—The nerves of the kidney are derived from the renal plexus and the lesser splanchnic. They pass into the renal structure with the bloodvessels; and, according to Pflüger, they terminate in the nuclei of the cells. The nervous system, in all parts of the body, controls and regulates the circulation of the blood, and thus impressions upon the fibres of the renal plexus which surround the *tubuli contorti* must influence the secretion of urine, and especially the excretion of urinary products. Moreau, in 1868, pointed out that section of the splanchnic nerve was followed, as in cholera, by an intestinal flux; and Eckhardt, in experiments which he also performed on the splanchnics, found that their section induced hyperæmia of the *tubuli contorti*, albuminuria and increased secretion of urine. Vascular tension, or blood pressure, is one of the physiological factors in the secretion of urine, and thus we have it artificially augmented to an abnormal degree. Hyperæmia of the kidney occurs likewise in cases of spinal paralysis, and particularly when the ganglionic nerves are affected. Vulpian found, as the result of observations on a dog subjected to the influence of woorara, that division of the left splanchnic was followed by congestion of the corresponding kidney, the organ assuming a deeper hue, becoming enlarged, and polyuria and albuminuria supervening. The influence of the vaso-constrictor nerves is thereby suspended. The contrary condition, anuria, is brought about by an opposite physiological state, contraction of the arterioles. In Vulpian's experiment there was no extravasation of globules of blood nor desquamation of the tubes. What was especially interesting, the renal vein became larger and redder. On the peripheric end of the cut nerve being subjected to the action of electricity, the kidney and its capsule became pale. They progressively resumed their reddish hue as the current was suspended, while the size of the renal vein diminished. Mental impression may act on the splanchnics in a similar manner, and hence we may witness

polyuria, and even hæmaturia. According to Byrni section of the cervical sympathetic diminishes the quantity of urine, while its electric excitation, on the contrary, augments it. Section of the pneumogastric seems to have no influence over the urinary secretion. Bernard states, however, that he has noticed in some experiments an augmentation of urine and a congestion of the kidney from excitation of the pneumogastric below the diaphragm. Arthaud and Butteau, on the contrary, observed an arrest of urinary secretion from excitation of the peripheric end of the pneumogastric. Section of the spinal marrow in the cervical region, by causing a lowering of blood-pressure, arrests urinary secretion. Excitation of the lower portion of the spinal cord produces the same result by contraction of the renal arterioles through the vaso-motor nerves. It is interesting to note, however, that if the splanchnics are previously divided, so as to eliminate vaso-motor action, excitation of the cord determines an augmentation of the secretion and an increase of arterial pressure. Pricking of the fourth ventricle causes polyuria and albuminuria, or glycosuria if the lesion be too high or too low. The physiological factors in the secretion of urine may be regarded as—(1) the function of the glomerulus—osmosis and dialysis; (2) the circulation of blood in the kidney—accelerated or slowed; and (3) vascular tension.

Generally speaking, the *blood in the capillaries of the glomerulus is subjected to a greater pressure, and that of the interstitial or parenchymatous capillaries of the kidney to a lesser amount of pressure* than the blood of ordinary capillaries. The intensity of the pressure is such that, as admitted by all physiologists, a purely mechanical filtration might take place, which would at least account for the first part of the urinary secretion; but on the nature of the fluid secreted there is a disagreement among authorities. Many theories have from time to time been enunciated as to the urinary secretion. The three which at present find most acceptance are those of Bowman, Ludwig and Kuss.

The Theory of Bowman.—According to Bowman, the glomerulus of Malpighi permits only the watery portion of the urine to filter through, the solid parts of the urine formed in the

kidney or taken from the blood being secreted by the cubical cells lining the convoluted tubes, and absorbed by, or incorporated with, the water as it passes along the tubes. Recognising the difficulty of comprehending how the very diffusible salts of the blood found in the urine did not pass through the tuft-walls and capsule with the water, Bowman himself and Von Wittich and Donders so modified the theory as to include the filtration of the diffusible salines with the water, while the epithelial cells of the convoluted tubes only secreted the urea and the uric acid. Recently Heidenhain has reverted to the opinion of Bowman, endeavouring to establish the independent elimination of the watery and the solid portions of the urine. These two processes seem really to take place in two different portions of the kidney. According to Heidenhain, the secretion of water by the kidney may be completely arrested without interfering with the elimination of solid substances injected into the blood, such as indigotate and urate of soda. This elimination takes place through the epithelium of the convoluted tubes and the larger branch of the loop of Henle. If the cortical substance of the kidney be eauterized, the secretion of urine is suspended in the portion thus operated upon; and even in the corresponding region of the medullary substance, whose canals in this case do not contain indigotate of soda. Under these circumstances, however, Heidenhain has found the cortical canals to be filled with this colouring matter; but the secretion of water having been arrested, the colouring matter was not drawn into the medullary canals. Hence, it is evident that the aqueous part of the urinary secretion transudes through the glomerulus, and presumably also from the convoluted tubes. Further, other considerations seem to point to the secretion of the watery portion of the urine by all portions of the kidney, the cortical as well as the medullary substance. In amphibious animals the glomeruli and the renal canaliculi have an absolutely distinct circulation, the glomerulus receiving its blood from the aorta, and the canaliculi from a portal system analogous to that of the liver, composed of venous branches proceeding from the inferior extremity, the oviduct and the dorso-lumbar vein. These are the afferent renal veins. If

the common aorta be tied, the glomeruli receive no blood, and consequently their function is brought to a standstill.

Theory of Ludwig.—According to this theory, blood-pressure performs the principal rôle in the secretion of the urine. Under the influence of this pressure, the serum of the blood transudes through the walls of the capillaries of the glomerulus minus the albuminates and the fats. The fluid which escapes contains water, salts of the blood, and extractive matters. Having reached the canaliculi, this liquid finds itself in contact with the epithelium of the convoluted tubes, and with the lymph which surrounds the canals, and which is a more concentrated fluid. The lymphatics and the capillaries which surround the canaliculi take up a portion of the water and salts filtered, until the endosmotic equilibrium is established. Ludwig primarily ascribes no rôle to glandular activity, and the experiments of Goll tend to show that blood-pressure alone is the chief factor in the process of urinary transudation. The quantity of urine augments with pressure, and its concentration is in an inverse ratio to the rapidity of the secretion, and never exceeds a certain figure. All this notwithstanding, the proportion of the urinary principles and of the blood cannot be explained on purely physical laws. And hence, even admitting the theory of Ludwig, the element of glandular activity requires to be invoked. An outstanding difficulty of this theory is the question why the albumen of the blood does not pass through the glomerulus with the other constituents. Ludwig's explanation of this is that the albumen diffuses with great difficulty in presence of the free acid of the urine which is formed in the kidney; but it is not in the glomerulus that this acid is formed, and it is here that the filtration takes place. Normally the albumen does *not* transude under two circumstances: Firstly, when the blood is healthy, the tissues being then consequently healthy; secondly, when there is neither undue delay nor undue pressure in the capillaries (we know that *albuminoids* will traverse animal membranes under undue pressure); conversely albumen will pass through the glomerular epithelium and the Malpighian capsule under the opposite conditions. Otherwise it seems to me that we should simply regard this as one of the ultimate facts of the organism—as constituting

one of the vital correlations—for which we have no satisfactory explanation to offer. Another difficulty presented by the theory of filtration is the enormous quantity of liquid which must traverse and be taken into the blood in order to furnish the proportion of urea eliminated in twenty-four hours. Besides, if this theory were correct, there ought to be a parallelism between the quantity of urine and the amount of urea excreted; but in certain cases this does not obtain. In diminishing, for instance, the calibre of the renal artery, the urea relatively diminishes in the urine. In fine, according to the theory of Ludwig, the transudation from the capillary vessels ought to cease when the concentration of the urine should become equal to that of the blood plasma. There would be thus a limit to the concentration of the urine, and it could never become more concentrated than the blood plasma. Hoppe-Seyler found, however, in putting the urine and the serum of the blood of a dog in an endosmometer, that the volume of the urine augmented by withdrawing water from the serum of the blood. It was thus more concentrated than the latter. In this case, however, any influence due to the fibrine is not taken into account. Ribbert, in order to determine whether the urine secreted by the glomerulus becomes concentrated in the convoluted tubes in rabbits, extirpated the medullary substance, and found that the amount of urine was greater. His experiments tended in favour of the resorption theory.

The Theory of Kuss.—In some respects the theory of Kuss is similar to that of Ludwig, only he evades the difficulty which we have just seen to be presented by the theory of Ludwig, Kuss maintaining that the whole serum filters through the glomerulus, as in the case of ordinary serous transudation. Hence, as the fluid passes along the convoluted tubes, according to him, the albumen is reabsorbed. The urine then would consist of serum less albumen. This looks a particularly clumsy operation on the part of nature, in all things so conservative of material, of force, and of energy. This resorption Kuss holds would be due to the vital activity of the epithelial cells, aided by the feeble pressure of the blood in the perieanalicular capillaries. This theory is held to explain how cysts of the kidney, formed in consequence of obliteration of the convoluted tubes, are not found to

contain urine, but an albuminous serous fluid, and how in these cases, or when the epithelium of the kidney is diseased, it is unable to resorb the albumen and it thus appears in the urine. It has been found that when albumen has been injected into the blood of rabbits it is eliminated by the glomerulus, and that the same thing happens after temporary ligature of the renal artery. It must be borne in mind that here we are dealing with a pathological condition, and that we must not too hastily draw conclusions from such data as to normal states and functions. It is thus evident that all the three theories—the three most usually accepted—present difficulties.

Pressure of blood is the main factor in determining the amount of the urinary secretion. In order that this secretion take place, the pressure, it is obvious, must be greater than the pressure in the convoluted tubes. It is thus the difference between the two pressures, and the excess of the former over the latter, which determines the secretion. When this difference of pressure is diminished or equalized, either by diminishing the blood-pressure by section of the cord, or by copious bleeding, or by augmenting the pressure in the canaliculi, as when the ureter is ligatured, the secretion of urine diminishes or is totally arrested. The inverse result is produced when the difference is increased, as when the blood-pressure is experimentally augmented by ligature of the aorta below the renal artery, the injection of water into the blood, and contraction of the cutaneous vessels, as from cold, etc. The pressure in the renal artery amounts to 120 to 130 millimetres of mercury.

All causes which influence the pressure of blood in the renal artery act indirectly on the urinary secretion. Thus, the quantity of urine is augmented simply by increased cardiac activity, and by diminution of the total vascular area, by an augmented amount of blood, as from large draughts of water, injection of water into the veins, etc. The secretion is diminished by opposite causes, such as diminution of the activity of the heart, excitation of the pneumogastric, the action of heat upon the skin, copious sweating, etc. Augmentation of blood-pressure not only raises the amount of urine, but it likewise increases the amount of solid constituents of the urine, though in feebler pro-

portion. According to Heidenhain, and in this he is supported by Paneth and Munck, the augmented pressure acts by accelerating the passage of blood through the glomerulus.

Epitome of the Relation between Urinary Secretion and Arterial Pressure.*

A. Secretion of urine may be increased :

(a) By increase of the general blood-pressure—by

- (1) Increase of the force or frequency of heart-beat (digitalis, alcohol, etc.),*
- (2) Constriction of the small arteries in other areas than that of the kidney (skin from cold, etc.).*

(b) By increasing the local blood-pressure, by relaxation of the renal artery without compensating relaxation elsewhere :

- (1) Division of the renal nerves (causing polyuria).*
- (2) Division of the renal nerves and stimulation of the cord below the medulla (causing greater polyuria).*
- (3) Division of the splanchnic nerves. As these nerves are distributed to other regions, other vessels are dilated besides the renal artery, and the polyuria is consequently less than in 1 and 2.*
- (4) Puncture of the floor of the fourth ventricle, or mechanical irritation of the superior cervical ganglion of the sympathetic. The renal arteries are thus dilated.*

B. Secretion of urine may be diminished :

(a) By diminishing the blood-pressure—by

- (1) Diminution of the force or frequency of the heart-beats.*
- (2) Dilatation of vessels in other areas than the kidney (skin in hot weather).*

* Kirkes' 'Physiology.'

- (3) Division of the cord below the medulla, causing vascular dilatation of the abdominal area and suppression of urine.
- (b) By increasing the blood-pressure by stimulation of the spinal cord below the medulla, when the constriction of the renal artery is not compensated for by general increase of the blood-pressure.
- (c) By constriction of the renal artery, by stimulating the renal or splanchnic nerves or the spinal cord.

The *condition* of the blood exercises a not less marked influence on the secretion of urine. In the normal condition the composition of blood oscillates within a certain range. Whenever this range is exceeded, that is to say, whenever any constituent is found in excess in the blood, even if it be a normal constituent, such principle is eliminated by the kidney, though not normally so eliminated. Thus, if an excess of albumen be taken into the blood, as may happen from an excessive indulgence, for instance, in raw eggs, albumen is found in the urine. What I have been in the habit of terming the vital correlation is disturbed, and *qua* this a pathological state is induced. If the theory of Kuss be the correct one, it is difficult to see why the albumen in this case is not absorbed by the epithelium of the convoluted tubes. It is in this manner that draughts of water augment the watery portion of the urine, the specific gravity of the blood being restored to its normal equipoise. Similarly, chloride of sodium, phosphate of soda, and most other salines, thus appear in the urine in proportion to the dose administered. Glycosuria shows itself when the glycose exceeds 0.6 per 100 in the blood. Finally, all diffusible substances introduced into the organism rapidly pass into the urine. As the nature of the urine thus depends on alimentation, why the secretion of herbivora and carnivora is different, and how, is apparent. The urine is thus a depuratory and antitoxic secretion. Hence, when nephrectomy or ligature of the ureter is practised, toxic manifestations appear more rapidly; and, conversely, when the urinary secretion is active, poisonous manifestations are retarded and mitigated. When the

urinary passages eliminate the poison to the extent that it is ingested, toxic phenomena do not appear at all. This happens, according to Bernard and Hermann, when *curara* is introduced into the stomach. The rôle of cellular activity on the secretion of urine is undoubted, as shown by experiments, and especially by artificial stimulation of the kidney. If the urinary secretion be arrested by diminishing the blood-pressure by section of the cord, or by retarding the venous circulation of the kidney, secretion may be re-established by the employment of certain diuretics, such as acetate of soda, urea, etc. Abeles found that when he added to the blood of the kidney blood unimixed with urea, not a drop of blood flowed from the ureter; but when he added blood to which urea had been added, the blood flowed more quickly, and urine was secreted. Abeles therefore infers that urea paralyzes the vaso-constrictor nerves, and excites the vaso-dilators of the kidney; but the subsequent experiments of Munck and Phillips seem to demonstrate that the effect is specially on the secretory cells. The influence of the epithelial cells is further demonstrated by the mode of action of the different salts of the urine. Senator and Munck have shown that if the venous circulation of the kidney be arrested at the same time that the quantity of urine diminishes, the proportion per cent. of urea diminishes, while the proportion per cent. of chloride of sodium does not vary. Lepine and Aubert found that by temporarily occluding the ureter of one side, and comparing the secretion of the two kidneys, that of the side operated on was more concentrated and the phosphates were less perfectly eliminated, but the chloride of sodium was eliminated as well as on the sound side.

Urine normally appears as a pale, straw-coloured and transparent fluid. It is an excrementitious liquid, representing the unutilized material introduced into the organism for the purpose of nutrition, as well as the products of organic disassimilation. The terms 'transparency' and 'aspect' of urine are often confounded. 'Aspect' obviously refers to the naked-eye appearance, and 'transparency' to transmissibility of light.

Transparency.—When passed, normal urine is usually clear and transparent. After a period of repose flakes of mucus

often appear, which, according to the density of the urine, either remain suspended in the fluid or are deposited. This mucus in the normal condition scarcely affects the transparency of the urine, but in certain affections of the urinary organs its amount may be so great as to render the urine opaque. This mucus is composed of epithelial débris from the bladder, the ureters, and the pelvis of the kidney. Frequently the urine becomes turbid when exposed to a low temperature, owing to the precipitation of bodies normally held in solution at a higher temperature. Again, loss of transparency may be due to the presence of adventitious chemical compounds only found in a pathological state, such as earthy phosphates of calcium and magnesium (in abnormal amount), and such constituents as pus and chyle.

Odour.—In the normal condition fresh urine has a peculiar aromatic odour. The smell of urine is said to be due to the presence of phenylic, taurylic and damoluric acids. The urine in diabetes has a sweetish, hay-like smell. Urine containing cystin has a smell similar to that of sweetbriar, which afterwards becomes very disagreeable. Certain medicaments impart their odour to the urine, such as turpentine (which imparts to it the smell of sweet-violets), copaiba, cubebs, oil of santal-wood, asparagus and garlic. When the urine contains decomposing blood or pus it has a putrid odour; and when it has undergone decomposition in the bladder it exhales an ammoniacal odour, and sometimes gives off sulphuretted hydrogen.

Colour.—The colour of urine varies according to concentration or dilution, to the presence of pathological pigments and to variations in dieting. It usually ranges from a pale straw-colour to a reddish yellow. The morning urine, which is called the *urina sanguinis*, is of a deeper colour than that emitted during the day or after the injection of large draughts of water—the *urina potus*. Occupying an intermediate place between these two in respect of colour, we have the urine evacuated some time after a repast—the *urina chyli*. The urine of the infant is generally paler than that of the adult, and during the first hours of existence it is entirely colourless. In acute febrile maladies, the colour of the urine is intensely deep,

varying from a deep yellow to the reddish-brown colour observed in certain chronic affections. In diabetes, hysteria, anæmia, and granular kidney, it is usually pale. Here there is polyuria; and in the case of the granular kidney the urine is of low specific gravity, as the convoluted tubes are to so great an extent denuded of their epithelium, and the chief constituents of the urine are consequently not eliminated (Black's 'Lectures on Bright's Disease,' p. 82). In nervous affections the urine is frequently colourless (*urina spastica*). In affections of the liver and biliary passages, the presence of bile pigments in the urine occasions a yellowish-green or brownish-green colour (icteric urine). It may also be observed that in being thus eliminated the bile pigments set up so much irritation as to cause the appearance of yellowish tube-casts in the urine. The presence of blood gives to the urine a more or less intense red colour, as we find it in the early stages of acute nephritis, calculous nephritis, cancer of the bladder, etc. In the condition termed hæmoglobinuria, hæmoglobin exists in the urine, which is thus coloured red. In certain cases of melanotic cancer the urine is coloured black. Certain medicaments alter its colour. Thus, santonin, rhubarb (crysophanic acid) and senna impart to it a yellowish colour. Saffron causes it to become of a greenish colour. The coloration caused by the pigments of senna and of rhubarb is not unlike that occasioned by the presence of blood, but it is easy to establish the distinction. The urine coloured by the former becomes more limpid and clearer in contact with a mineral acid, while that by the latter does not become clearer, but rather becomes of a deeper colour. Further, urine containing pigments of rhubarb and of senna give with ammonia or with potash a purple colour. The yellowish coloration due to santonin oscillates from yellowish-red to a reddish-purple in presence of an alkali.

Krukenberg gives the following table as to urine colours :*

PATHOLOGICAL AND OTHER URINE COLOURS.

COLOUR OF URINE.	CAUSE OF COLORATION.	PATHOLOGICAL CONDITION.
Pale yellow to colourless.	Diminution of normal pigments.	Anæmia, chlorosis, diabetes, and other nervous attacks.
Dark yellow to brown red, easily depositing a sediment.	Increase of normal or occurrence of pathological pigments.	Acute febrile diseases.
Yellowish and milky.	Fatty drops floating in urine.	Chyluria.
	Suspended pus corpuscles.	Pyelitis, or other purulent disease.
Green, or yellow green.	Bile-colouring matter.	Jaundice.
Greenish-yellow; later greenish-brown, or approaching black.	Decomposed hæmoglobin and various chromogens. Carbolic acid urine is similar.	Hæmorrhage into the kidneys in long-continued intermittent fever; also melanotic cancer.
Red or reddish.	Unchanged hæmoglobin.	Hæmorrhage, or hæmoglobinuria.
	Pigments which are taken up with the food, such as madder, bilberries, logwood, fuchsin, etc.	
Brown.	Bile-colouring matters and methæmoglobin.	
Brown-yellow to red-brown, becoming blood-red on adding alkalis.	Substances which are introduced into the organism with senna, rhubarb, chelidonium, etc.	

Fluorescence, Temperature, etc.—Normal urine is slightly fluorescent. With pale urine the fluorescence is bluish; with reddish-yellow it is green or yellow. Albuminous urine is more fluorescent than normal urine, and urine which has become

* *Grundriss d. Med. Chem. Analyse*, 1884, S. 78.

alkaline more than undecomposed urine. All normal urines cause a right deviation of the plane of polarization. When the urine is albuminous the deviation is to the left. Saccharine urines cause a right-handed deviation proportionate to the quantity of sugar.

When the urine is agitated, a froth appears which rapidly disappears on repose. With albuminous and saccharine urines the froth is more abundant and disappears more slowly. The normal temperature of urine is about 37° C.; but in certain acute affections, such as pneumonia, scarlatina, rheumatism, etc., the temperature rises correspondingly with that of the body. In cases of idiopathic tetanus, it may rise as high as 44° C., and fall as low as 26° C. in cases of tubercular meningitis.

According to Feltz, Ritter, Bouchard, etc., normal urine is toxic. If from 90 to 100 grammes be injected into the veins of a rabbit weighing 2 kilogrammes, the animal is poisoned by lowering of its temperature. The toxicity of the urine depends on various circumstances; for example, cerebral activity, muscular activity, sleep, alimentation, etc. Pathological urines are not necessarily more toxic than the normal. They may even be less toxic. In nephritis the urine is not more toxic than distilled water, a circumstance doubtless due to the very small amount of urinary constituents contained in the urine, especially in that of the granular kidney.

Quantity of Urine. — The amount of urine secreted in twenty-four hours averages in a healthy male individual from 1,400 to 1,500 c.c.,* or from 49 to 50 ounces. In the female the volume is less. It oscillates between 1,000 and 1,200 c.c. For obvious reasons, the amount is diminished when the skin is active, and *vice-versâ*. Contraction of the cutaneous vessels, as from cold, etc., stimulates and augments the secretion of urine. The smallest amount is secreted between 2 a.m. and 4 a.m., and the greatest between 2 p.m. and 4 p.m. If the average quantity of urine secreted be compared with the weight of the body, we find that for each kilogramme there is eliminated, on an average, 1 c.c. of urine per hour. In the aged the volume is less. The quantity secreted by the infant at the

* 100 c.c. = $3\frac{1}{2}$ ounces.

breast, compared with its body-weight, is three or four times greater than in the case of the adult.

As a rule, the largest amount of urine is eliminated about two hours after a repast, the least during the night, and the medium amount in the morning. The secretion is augmented by abundant draughts, such as of ordinary water, beer, coffee, and water holding salines in solution. If after large draughts of water violent exercise be indulged in, the augmentation of the volume of the urine is less, as much of the fluid is eliminated by cutaneous transpiration. During winter, when the pulmonary and cutaneous exhalations are much less abundant than in summer, a greater quantity of urine is secreted and *vice-versâ*. Excitable individuals secrete more urine, and in most people nervous excitement is attended with increased micturition. The urinary secretion is less when the amount of fluids ingested is diminished. After parturition, when the secretion of milk commences, the quantity of urine secreted diminishes.

Hydruria and Polyuria. — Under certain circumstances patients pass from 10 to 12 litres of urine in twenty-four hours. There then exists polyuria, and of this state two varieties are recognised :

First, Polyuria properly so called, which is divided into saccharine or diabetic polyuria, and the polyuria of diabetes insipidus, when there is no sugar in the urine.

Second, Simple Hydruria.

In the first case, the percentage of solid matters to the litre of urine is either normal, or sometimes augmented. In the second case the fluid matters are almost normal in relation to the amount passed in twenty-four hours, while feeble in proportion to the litre. In this case there is no hypersecretion of solid matters, but there is a dilution of them by the abnormal amount of water. Certain medicinal agents exercise a marked influence over the urinary secretion. The diuretics markedly augment the secretion, and of these the most important are alcohol, nitrous ether, nitrate and acetate of potash, squills, digitalis, broom, caffeine, etc. Certain other medicines diminish the urinary secretion, such as opium (and especially its alkaloid, codeia), belladonna, salts of iron and copper (especially the citrate of iron with

quinine), ammonia-citrate of iron, etc. Cantharides and arsenic may entirely suppress the urinary secretion.

Pathological States influence the quantity of urine. In acute febrile affections, as in pneumonia, pleurisy, typhoid fever, and acute muscular rheumatism, the quantity is markedly diminished; it then augments as the intensity of the disease diminishes, and during convalescence it becomes normal, and sometimes greater in quantity than in health. In cases of anæmia, profuse loss of blood, and in cholera the quantity is very much diminished. In cholera the diminution frequently amounts almost to *anuria*, and this condition may continue for days, to be followed by *polyuria*. The urine is likewise diminished in dropsies, gout, and atrophic cirrhosis of the liver. In the various forms of diabetes, as from glycosuria, phosphaturia, etc., the quantity of urine is always augmented.

Variations of Density and of Solid Residue in Disease.—

In most acute and chronic diseases, both the density of the urine and the amount of solid residue undergo great variations, which, from the point of view of diagnosis, are of primary importance. In the majority of acute affections the urine passed is markedly concentrated, sometimes attaining to a density of 1035. This is chiefly due to the augmented excretion of urea, sulphates, and alkaline phosphates. We find the same condition in chronic affections, where there is disturbance of normal metamorphosis, as in diabetes, gout, etc. In diabetes the urine may attain a density of 1050.

In certain forms of Bright's disease* (the cirrhotic kidney), and in the amyloid forms of kidney disease, the specific gravity of the urine is very low. It sometimes descends to a specific gravity of 1005, or 1004. The excretion of urea is here diminished, owing to desquamation of the cells of the convoluted tubes. The specific gravity is also diminished in cases of polyuria and simple hydruria, and likewise in most nervous affections attended with excitement.

The Specific Gravity of the urine in the normal state ranges from 1015 to 1025. After excessive draughts of water it has

* *Vide* 'Lectures on Bright's Disease,' by Auth.or. J. and A. Churchill, London.

been known to sink as low as 1002; and according to Dr. W. G. Smith, it has risen after great sweating and forced marches from 1035 to 1040. The specific gravity in infants is as low as from 1003 to 1006. The average normal density may be taken as 1020. The average density in the female is somewhat less. It may be regarded as 1016. The density varies with the time of the day, and the nature of the alimentary substances ingested, muscular activity, etc. A healthy adult male excretes about 70 grammes, or $2\frac{1}{2}$ ounces, of solids in his urine *per diem*.

Determination of the Density of Urine.—In practice the determination of the density of urine is determined by means of the *urinometer*. This instrument is so graduated as to indicate to half a degree a density varying from 1000, that of water, to 1040, beyond which the density of urine rarely passes. Urinometers are generally graduated for a temperature of 15° C. Where absolute accuracy is necessary, the urine must be of this temperature. If the urine be in quantity insufficient for the employment of the urinometer, the specific gravity may be obtained by weighing by means of a small flask, the *picnometer*. Let P be the weight of a given volume of urine, and p the weight of an equal volume of distilled water at the same temperature; then P divided by p will give the density of the urine.

$$D = \frac{P \text{ Weight of urine.}}{p \text{ Weight of water.}}$$

By means of the hydrostatic balance of Mohr the specific gravity may be obtained with greater precision and rapidity.

Estimation of the Total Solids of the Urine.—An approximate to the total solids of the urine may be obtained by means of what is known in this country as Christison's formula, and abroad as that of Hæser or Trapp. If the last two figures of the specific gravity as expressed in four figures be multiplied by 2·33 (Christison and Hæser), or by 2 (Trapp), the result will give in grammes the total solids in 1,000 c.c. The weight of the *solid residue* of the urine, or the amount of solids which the urine holds in solution, averages 47 grammes per litre in a healthy man, and 37 in the female. This residue is composed of *organic*

and *mineral substances*. The former always exist, in the normal condition, in greatest abundance. In order accurately to determine the amount of these solids, 10 c.c. to 15 c.c. of urine are measured by means of a pipette, and are allowed to flow into a glass vessel, which is to be hermetically sealed, and whose weight has been previously determined. The capsule is then heated to desiccation. The capsule and contents are now weighed, after having been allowed to cool, in juxtaposition to sulphuric acid, under a glass shade. From the weight thus obtained that of the capsule is deducted, and the weight of the dry residue is then determined.

This procedure, however, does not give absolutely accurate results, for in the process of evaporation at 100°C. , and desiccation at 105°C. , a certain amount of ammonia resulting from the decomposition of urea is given off. In order to obviate this, from 1 to 2 grammes of urine are to be weighed between two watch-glasses. The upper one is then removed, and the lower one, containing the urine, is placed in a vacuum in presence of sulphuric acid. After the space of twenty-four hours, a new weighing is made to determine the exact amount of the solid residue. If it is desired to determine separately the proportion of *mineral substances* as apart from the proportion of *organic substances* contained in the residue of the urine, it suffices to destroy the latter by incineration. In this case a platinum crucible must be employed, and careful weighing be resorted to.

Reaction of Normal Urine.—Normal urine always possesses an acid reaction. It reddens blue litmus. This reaction is only rarely due to the presence of a free acid. It ought rather in most instances to be attributed to acid phosphate of soda. It may, however, be occasionally due to combinations of uric, hippuric, and lactic acids. In the normal condition the degree of acidity is not uniform. The urine secreted during the night is more acid; that passed after a meal is less acid. Milk diet and alcoholic beverages augment the acidity, and vegetable diet and abstinence diminish it.

Determination of the Degree of Acidity.—The degree of acidity of urine is determined by comparing the saturating power of urine with that of an acid, such as oxalic acid. With

this view we find out how much of the latter corresponds to the non-saturated acid contained in a measured quantity of urine by neutralizing it with an alkaline solution, of which each cubic centimetre represents a determined quantity of oxalic acid. An alkaline solution of caustic soda is employed so diluted that each c.c. corresponds to 10 milligrammes of oxalic acid. The acid solution is prepared by dissolving 1 gramme of non-effloresced pure oxalic acid in 100 c.c. of distilled water. Hence is obtained a liquor containing in each c.c. 10 milligrammes of oxalic acid. Of a given specimen of urine to be tested, 100 c.c. are placed in a glass vessel, and by means of a burette the soda solution is added drop by drop. After the addition of every demi-cubic centimetre, the liquid is stirred with a glass rod, and one drop of the solution is then removed and placed on a piece of blue litmus paper. If the reaction is still acid, as manifested by a reddening of the paper, the soda solution is added until this reaction is no longer produced. The number of c.c. of the soda solution necessary to neutralize the urine is then noted. It is thus easy to calculate how much oxalic acid corresponds to the acidity of 100 c.c. of the urine, for we know that 1 c.c. of the soda solution corresponds to 10 milligrammes of oxalic acid. If, for example, 12 c.c. of the soda solution were required to neutralize 100 c.c. of the urine; then $0.10 \times 12 = 0.12$ grammes of oxalic acid. Otherwise, the estimation of the acidity of the urine may be obtained by means of this standard solution, and a solution of phenolphthalein, by which the point of neutralization is indicated. Phenolphthalein, one of the coal-tar products, is devoid of colour in the acid and neutral states, but becomes of a deep magenta colour in presence of an alkali. The standard solution of soda is the normal volumetric solution of the British Pharmacopœia, of which 100 c.c. are made up to a litre. The litre contains 40 grammes of pure caustic soda, and each c.c. of this solution represents an equivalent of 0.063 grammes of crystallized oxalic acid.

Mode of Estimation.—Place 10 c.c. of the urine to be examined into a porcelain dish, and add two or three drops of phenolphthalein solution. This solution is made by dissolving 0.2 to 0.3 grammes in 100 c.c. of alcohol. From a 10 c.c.

measure graduated to tenths of a c.c., drop into the urine the soda solution, constantly stirring, until the permanent pink tinge has been produced, which indicates that the acidity has been overcome. Read off the amount of the standard solution, each c.c. of which corresponds to .0063 grammes of crystallized oxalic acid; then the number of c.c. of the soda solution multiplied by .0063 will represent the acidity expressed as grammes of crystallized oxalic acid per 10, and this result multiplied by 100 will represent the acidity per 1,000 of urine.

Table showing the Amount of Acidity,
expressed as Oxalic Acid in parts (by weight) per 1,000 (by volume)
for the number of c.c. of decinormal Alkali required to neutralize
10 c.c. of Urine.

C. C. to Neutralize	Oxalic Acid grammes per 1,000 c.c.	C. C. to Neutralize	Oxalic Acid grammes per 1,000 c.c.	C. C. to Neutralize	Oxalic Acid grammes per 1,000 c.c.
0.1	0.063	4.6	2.898	9.1	5.733
0.2	0.126	4.7	2.961	9.2	5.796
0.3	0.189	4.8	3.024	9.3	5.859
0.4	0.252	4.9	3.087	9.4	5.922
0.5	0.315	5.0	3.150	9.5	5.985
0.6	0.378	5.1	3.213	9.6	6.048
0.7	0.441	5.2	3.276	9.7	6.111
0.8	0.504	5.3	3.339	9.8	6.174
0.9	0.567	5.4	3.402	9.9	6.237
1.0	0.630	5.5	3.465	10.0	6.300
1.1	0.693	5.6	3.528	10.1	6.363
1.2	0.756	5.7	3.591	10.2	6.426
1.3	0.819	5.8	3.654	10.3	6.489
1.4	0.882	5.9	3.717	10.4	6.552
1.5	0.946	6.0	3.780	10.5	6.615
1.6	1.008	6.1	3.843	10.6	6.678
1.7	1.071	6.2	3.906	10.7	6.741
1.8	1.134	6.3	3.969	10.8	6.804
1.9	1.197	6.4	4.032	10.9	6.867
2.0	1.260	6.5	4.095	11.0	6.930
2.1	1.323	6.6	4.158	11.1	6.993
2.2	1.386	6.7	4.221	11.2	7.056
2.3	1.449	6.8	4.284	11.3	7.119
2.4	1.512	6.9	4.347	11.4	7.182
2.5	1.575	7.0	4.410	11.5	7.245
2.6	1.638	7.1	4.473	11.6	7.308
2.7	1.701	7.2	4.536	11.7	7.371
2.8	1.764	7.3	4.599	11.8	7.434
2.9	1.827	7.4	4.662	11.9	7.497
3.0	1.890	7.5	4.725	12.0	7.560
3.1	1.953	7.6	4.788	12.1	7.623
3.2	2.016	7.7	4.851	12.2	7.686
3.3	2.079	7.8	4.914	12.3	7.749
3.4	2.142	7.9	4.977	12.4	7.812
3.5	2.205	8.0	5.040	12.5	7.875
3.6	2.268	8.1	5.103	12.6	7.938
3.7	2.331	8.2	5.166	12.7	8.001
3.8	2.394	8.3	5.229	12.8	8.064
3.9	2.457	8.4	5.292	12.9	8.127
4.0	2.520	8.5	5.355	13.0	8.190
4.1	2.583	8.6	5.418	13.1	8.253
4.2	2.646	8.7	5.481	13.2	8.316
4.3	2.709	8.8	5.544	13.3	8.379
4.4	2.772	8.9	5.607	13.4	8.442
4.5	2.835	9.0	5.670	13.5	8.505

Or let a solution of oxalic acid be made containing 6·3 grammes per litre in distilled water. Put into a glass vessel 10 c.c. of this standard acid solution, adding three drops of an alcoholic solution, of phenol-phthalein, and determine the volume N of a dilute alkaline solution of potash or soda requisite to saturate the acid solution. The 10 c.c. of the oxalic acid solution contain 63 milligrammes of oxalic acid, or an equivalent of 49 H_2SO_4 . The alkaline solution is added by means of a graduated burette. Read off the number N of c.c. used to neutralize the acid. This being done, repeat the operation, putting into the glass vessel 10 c.c. of the urine, instead of the acid solution, and having added the alkaline solution until the earthy phosphates show a milkiness, add three drops of phenol-phthalein solution, and then continue the addition of the alkaline solution until a persistent rose-tint appears. Then read off the number of c.c. of the alkaline solution required to effect this change; hence

$$N : 49 :: N'' : x.$$

Estimation of the Alkalinity of the Urine.—The estimate of the alkalinity of the urine is determined by its power of neutralizing a solution of oxalic acid, every 10 c.c. ($\frac{N}{10}$) of which are equivalent to 17 milligrammes of ammonia. Place 10 c.c. of the acid solution in a glass jar, and from a burette add the urine.

Variations in the Reaction of the Urine.—Certain medicinal agencies modify the reaction of the urine; alkalies, alkaline carbonates, and vegetable acids (converted in the system into carbonates), render it alkaline. In typhoid fever the acidity is much above the normal. It augments with the intensity of the fever, and diminishes as the fever disappears, the urine becoming alkaline during convalescence. The same thing obtains in cases of pneumonia, pleurisy, rheumatism, etc. In diabetes and rickets there is preternatural acidity. Mineral acids, being often eliminated without undergoing change, render the urine acid.

In cases of general debility, chloro-anæmia, and depressing affections of the nervous system, the urine is slightly alkaline. When the vegetable acids are taken in large quantity, the

earthly phosphates may be precipitated. In this case an alkaline reaction is imparted to reddened litmus. This blue colour persists after desiccation. It is otherwise, however, if the alkalinity be due to the decomposition of urea, and its transformation into carbonate of ammonia. In this case the litmus which has become blue becomes red if heated, owing to the volatilization of carbonate of ammonia, and a glass tube moistened with hydrochloric acid evolves white vapour if held above the urine (chloride of ammonium). The alkaline fermentation of urea may take place in the bladder, and then the urine is alkaline when voided. It exhales a fœtid odour, and usually contains a deposit of pus, with crystals of triple phosphates, urate of ammonia, and amorphous granulations of carbonates and phosphates of lime and magnesium. In cases of cystitis and paralysis of the bladder this is a frequent occurrence. Urine may be voided acid, and become alkaline on exposure to air.

Chemical Composition of the Urine.—Normal urine contains substances which, having served their purposes in the organism, fall to be eliminated as refuse products. Of these substances the *normal elements* of the urine comprise two groups, the one formed of *organic elements*, which are the products of retrogressive metamorphosis, the other of *inorganic elements*. They may be thus enumerated :

Organic Elements.—Urea, creatinine, creatine, xanthine, uric acid, allantoin, oxaluric acid, hippuric acid, benzoic acid, succinic acid, oxalic acid, phenols, sulphocyanic acid, colouring matters, mucine, and leucomaines.

Inorganic Elements.—Soda, potash, lime, magnesia, iron, combinations of hydrochloric, sulphuric and phosphoric acids, phospho-glyceric acid, silicic acid, ammonia, nitric and nitrous acids, peroxide of hydrogen, carbonic acid gas, oxygen and nitrogen.

The elements of the first group thus exist in greater abundance than the second. One kilogramme of urine contains these substances in the following proportions :

ORGANIC ELEMENTS = 32·114 grammes, consisting of

Urea	24·270 grammes.
Uric acid	0·400 „
Hippuric acid	1·000 „
Creatinine and creatine	1·000 „
Xanthine	0·004 „
Colouring matter	5·440 „

INORGANIC ELEMENTS = 15·530 grammes.

Chloride of sodium	10·231 grammes.
Alkaline sulphates	3·100 „
Alkaline phosphates	1·431 „
Alkaline phosphates of magnesia	0·455 „
Alkaline phosphates of lime	0·313 „

Toxicity of the Urine.—By injecting urine into the veins, he observed the following results: myosis, acceleration of the respiration, difficulty of movement (akinesis), somnolency, polyuria, disappearance of the corneal reflexes, and convulsions. It is not probable that these results bear any relation to the amount of urine injected, for in the case of pure water 122 c.c. per kilogramme are required to kill a rabbit; while the injection of 46 c.c. of normal urine causes death. The toxicity, therefore, is in the urinary constituents. Taking urica in an isolated form, Bouchard found that the intravenous injection of 6·43 gr. killed a rabbit. The mineral salts, and especially those of ammonia and potash, are very toxic. They cause convulsions. The toxicity of the urine is diminished by decolorization with carbon. It probably removes other constituents than pigments. That the toxicity of urine is not due to volatile principles is shown by its persistence after boiling. Bouchard has demonstrated that the matters soluble in water are less toxic than those which are soluble in alcohol. The latter cause coma, diuresis, and abundant ptyalism. The elements soluble in water cause convulsions and myosis. Urine secreted in the waking state is more toxic than that secreted during sleep; the latter is convulsive, the former narcotic. According to Bouchard, *uræmia* is a poisoning re-

sulting from all the urinary constituents, although in unequal proportions, accumulating in the blood through interrupted elimination by the kidney.

Pathological Sediments and Concretions.—The proportion of the normal constituents of the urine undergoes wide variation apart from that due to alimentation, age, sex, etc., in certain pathological conditions. Here there are found in the urine elements which it does not contain in the normal state, and which constitute an important diagnostic sign. Of these the most important are albumen, and other albuminoid bodies, such as globulin, hemialbumose, hæmoglobin, and peptones, sugars (especially glucose), elements of the bile (biliary acids, cholesterine, etc.), acetone, tyrosine, and leucine, cystine, fats, etc. All the normal and all the pathological elements are usually found in solution in the urine, but sometimes they are precipitated more or less quickly after micturition, or even in the urinary passages. The urine is said then to contain sediments whose examination should be carefully made. Sometimes these sediments are composed of insoluble pathological elements, which are never found dissolved in the urine. When these sediments form in the urinary passages, they may, instead of being eliminated, increase by accretion in the bladder or kidney and constitute calculi.

Accidental Elements of the Urine.—The greater portion of medicinal agents, either given as such or as poisons with criminal intent, are eliminated by the urine, and can be discovered there. These constitute the accidental elements which are of importance both to the physician and to the toxicologist.

Reactions of Normal Urine, and Significance.

It reddens blue litmus.	The urine is acid (acidity due usually to acid phosphate of sodium, rarely to free acid). Occasionally the acidity may be due to acid combinations of uric, hippuric, and lactic acids.	
	It evolves a gas which renders red litmus blue. The deposit contains triple phosphates (ammonio - phosphate of magnesia). It does not evolve gas. The deposit contains no triple phosphate.	
It renders red litmus paper blue.	The urine is alkaline. On being heated in a test-tube	The urine has become ammoniacal from decomposition of the urea $(3\text{CH}_4\text{N}_2\text{O} = \text{H}_3\text{C}_3\text{N}_3\text{O}_3 + 3\text{NH}_3)$ urea cyanuric ammonia acid
		<div> <div> The urine is alkaline when voided from the bladder. </div> <div> Sufficiently concentrated, on being treated with an acid it evolves a gas which renders lime-water turbid. </div> </div> <div> Alkalinity due to alkaline carbonates. </div> <div> Treated similarly, it does not evolve a gas. </div> <div> Alkalinity due to alkaline phosphates. </div>

1. A little hydrochloric acid added to a large quantity of urine (5 c.c. to 100) causes coloured crystals of uric acid of various shapes to separate out after ten or twelve hours.

A large quantity of hydrochloric acid added to a little urine (3 to 1) causes the formation of indigo blue and indigo red, the urine becoming pale red, then brownish-red, or violet to deep blue. This coloration may be due to the oxidation of other chromogens, such as compounds of skatol and the reducing substances.

2. If some urine be gently poured on the surface of common red nitric acid, a garnet-red zone forms at the surface of contact (Hiller's 'urophæin' ring), which is better seen against a white background. (In urines rich in uric acid, just over the ring there may be a white layer caused by the separation of urates, which may be mistaken for albumen.)

3. Caustic soda as well as ammonia precipitates out the phosphates of the alkaline earths, which separate partly in bunches of long needle-shaped crystals, partly in the amorphous form.

4. Warming with phospho-molybdic acid causes, after acidulation with nitric acid, a lively blue coloration, due to its action on the urates.

5. Iodized starch is decomposed by urine (presence of H_2O_2).

6. By adding mercuric nitrate in solution for some time a clouding arises, which disappears on agitation, due to the formation of sodium nitrate and perchloride of mercury ($[\text{NO}_3]_2\text{Hg} + 2\text{NaCl} = 2\text{NaNO}_3 + \text{HgCl}_2$) soluble in acid urine. After all the chloride of sodium is decomposed a permanent precipitate forms, due to a combination of the urea with a salt of mercury. (Basis of Liebig's method of estimating urea.)

7. Chloride of barium precipitates baric sulphate, BaSO_4 , and phosphate, $\text{Ba}_3(\text{PO}_4)_2$; when this precipitate is dissolved in hydrochloric acid a cloudiness is left.

8. Nitrate of silver precipitates silver chloride, AgCl , and phosphate, Ag_3PO_4 ; the latter first, afterwards all the chlorine in the urine, combines with the silver.

9. Lead acetate precipitates sulphate of lead, PbSO_4 , phosphate, $\text{Pb}_3(\text{PO}_4)_2$, and chloride, PbCl_2 , besides other substances.

10. Ferric chloride precipitates, after previously acidulating with acetic acid, phosphate of iron, $\text{Fe}_2(\text{PO}_4)_2$.

11. An ammoniacal solution of cupric oxide is decomposed by boiling by the action of the urates.

12. Tannic acid produces no precipitate with normal urine. (Krukenberg, *Grundriss d. Med. Chem. Analyse*, 1884.)

PART II.



CHAPTER II.

NORMAL ELEMENTS OF THE URINE.

History of Urea—Description—Physiological Conditions which modify the Amount of Urea—Chemistry—Artificial Production of Urea, etc.—Physical Properties—Combinations with Acids—Extraction and Preparation of Urea—Quantitative Analysis of Urea—Process of Léconte—Process of Millon—Process of Liebig—Volumetric Analysis—Hypobromite Process—Pathological Significance—Uræmia—Medicinal Agents which Influence the Excretion of Urea—Therapeutic Indications.

THE normal constituents of the urine are divisible into: (1) **Organic Substances**, (2) **Inorganic Substances**, and comprise the following:

ORGANIC SUBSTANCES.

Urea.
Uric acid (urates).
Hippuric acid.
Creatine and creatinine.
Xanthine and hypoxanthine.
Oxaluric acid.
Allantoine.
Succinic acid.
Benzoic acid.
Oxalic acid (oxalate of lime).
Volatile acids (phenols).
Colouring matters.

INORGANIC SUBSTANCES.

Chloride of sodium.
,, of potassium.
Sulphuric acid and sulphates.
Phosphoric acid and phosphates.
Phosphoglyceric acid.
Potash, soda, lime, and magnesia.
Ammoniacal salts.
Iron, silica, nitrates and nitrites.
Peroxide of hydrogen.
Carbonic acid, oxygen and nitrogen.

Nitrogenous Constituents (Organic).

		UREA.		Percentage composition.
CO(NH ₂) ₂	{ Carbon	12	12 × 1 = 12	20.00
	{ Hydrogen	4	1 × 4 = 4	6.66
	{ Nitrogen	28	14 × 2 = 28	46.67
	{ Oxygen	16	16 × 1 = 16	26.67
		<hr/> 60 = comb. wt.		<hr/> 100.00

History.—This substance, one of the most important constituents of the urine, was discovered by Boerhaave prior to 1720, but it seems to have attracted little attention until 1771, when it occurred to the younger Rouelle to extract with spirit of wine the ‘saponaceous matter’ or syrup obtained by the evaporation of urine. This extract he found to be crystallizable, and conceived that it contained hydrochloric acid as an essential ingredient. Prior to this, Boerhaave succeeded in separating the chloride of sodium and the urea. In 1798 Cruikshank obtained this principle in the form of crystal, but it was not until 1799 that Fourcroy and Vauquelin obtained it in a pure form, and recognised it as the crystallized substance of Rouelle. Berzelius was the first to obtain it in a colourless form by means of oxalic acid, and Prout ultimately established its composition.

Description.—Urea is one of the products of the perfect oxidation of nitrogenous tissue in the living body. Of the solid constituents of the urine it constitutes one half, while a fourth is made up of chloride of sodium. It exists in the urine of all the mammifera, birds, and reptiles, but it is in the urine of carnivorous animals that it exists in greatest abundance. It is formed in the blood, or, more strictly speaking, it is a product of the interchange of blood constituents with the nitrogenous textures of the body, and it is simply filtered from the system by the kidneys. This is demonstrated by the fact that when structural disorganization of the kidney supervenes on disease (as in Bright’s disease), urea and other excrementitious substances accumulate in the blood, and give rise to the form of blood-poisoning termed uræmia.

In the serous effusions which attend diseases of the kidney and in the sweat a much larger quantity of urea is found than in the normal condition. In cholera, which is attended with suppression of the urine and deficient oxidation of tissue, urea, in consequence, is found correspondingly diminished in the blood. No trace of urea is found in the muscular tissue or juice of muscle, but there are other nitrogenous substances representing a lower form of oxidation, such as creatine and xanthine, and from which urea can be produced. That such transformation takes place in the organism is shown when, by introducing such substances as uric acid, allantoine, and creatine into the blood, the quantity of urea is forthwith augmented in the urine. This transformation is effected by means of the oxygen and the alkalies of the blood.

Besides existing normally in the urine and in the blood (0.16 per 1,000, Picard), (0.177, Marchand), urea is found in the amniotic fluid, in the chyle, and lymph (2 per 1,000, Wartz), in the saliva (0.36 per 1,000, Picard; 0.67 to 1 per 1,000, Rabuteau).*

According to Rabuteau and Papillon, urea exists in notable quantity in the peritoneal cavity of flat fish under the form of trimethylurca, which, they point out, is decomposed under the influence of alkalies and ammonia into trimethylamine.

Alimentation exercises a direct influence over the amount of urea excreted from the body; for while upon a mixed diet 25 grammes per day may be eliminated (2.5 to 3.2 per cent.), the quantity may be increased to 50 grammes if a highly nitrogenous diet be indulged in. Lehmann found the quantity to amount to as much as 58 grammes in the twenty-four hours on a purely animal diet, and to decrease to 15 grammes on a non-nitrogenous diet. Urea does not disappear from the urine even when no food is taken. So strongly may the urine become impregnated with urea, that the mere addition of nitric acid to it, without evaporation, may determine the instant formation of nitrate of urea.

The question has been propounded whether it is necessary for the production of urea from nitrogenous principles that they be previously incorporated with the organism. It has been

* *Comptes Rendus de la Société de Biol.*, 1871, p. 180.

maintained* that certain nitrogenous principles of food are convertible into urea by the system without previous assimilation, just as sulphates and phosphates appear rapidly in the urine after the ingestion of a diet rich in sulphates and phosphates. In this manner it was concluded that a portion of the urea found in the urine is directly traceable to the food.

This opinion must be received with reservation, and for the following reasons: Urea is formed by the system even when no food whatever is taken, and its proportion diminishes but very little during the first days of fasting; it is notably increased by muscular exertion, and it is with much difficulty artificially formed from nitrogenous materials which have been subjected to the physiological processes of the body. Admitting that it does appear in augmented proportion in the urine after food, it seems more reasonable to suppose that the alimentary principles which find their way into the blood give a stimulus to the disintegration and oxidation of tissue, and that there is an accelerated circulation attendant on the process of digestion. It seems to me that it is in this relation that the augmented production of urea and alimentation ought to be regarded.

In a paper on this subject Dr. Salkowski† remarks that the principal facts are that certain amido-acids, after their ingestion in the alimentary canal, appear in the urine in the form of uramid acids, or combinations of the amido-acids with the group CONH. Secondly, certain other amido-acids, such as glycocoll, leucin, asparaginic acids, which are products of the disintegration of albumen, when administered with the food, lead to augmented excretion of urea, and after the ingestion of sal ammoniac the greater part of the nitrogen appears in the urine as urea.

Physiological Conditions which modify the Amount of Urea.—In the condition of health, the amount of urea in the urine varies at different periods of the day, and with the nature and quantity of food and exercise. As we have seen, it is augmented by nitrogenous diet and exercise; cold baths and intellectual activity (Byasson) are alleged to have a like influence. The

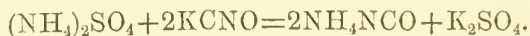
* *Comptes Rendus de la Société de Biol.*, 1871, p. 180.

† *Centralblatt*, No. 53, 1875.

quantity is diminished by repose and a vegetable diet. Rabuteau* has made the interesting observation that during menstruation the amount of urea is diminished by 20 per cent. The diminution appears two days before the appearance of the menses, and ceases a few days afterwards. During that time the pulse diminishes in frequency, and the temperature is lowered by about half a degree. This is a most interesting observation in view of the fact that while in man the amount of carbonic acid gas eliminated as he advances in life up to forty or fifty years of age augments, in woman, from the establishment of menstruation to the menopause, the amount of carbonic acid eliminated by the system is not greater than in the girl of fifteen. During twenty days of each month the adult female eliminates much more urea and carbonic acid than the non-menstruating girl. The female who eliminates from 14 to 15 grammes of urea during the period of menstruation eliminates from 19 to 20 grammes before menstruation and five or six days after it has ceased. Now, physiological data show that a direct relationship exists between the quantity of blood discharged from the system at this period and the amount of carbonic acid and urea formed; for, as we know, the red-blood corpuscles are the carriers of oxygen; it is through their agency that the nervous centres are stimulated, and it is by their means, through their oxygen, that eremacausis is carried on, and carbonic acid and urea produced.

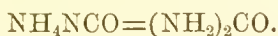
Generally speaking, an adult man eliminates in his urine from 18 to 30 grammes per day; a female, on an average, 25 grammes. Some authorities give a higher figure. Neubauer, in the case of an individual on a mixed diet, gives from 22 to 35 grammes, and Beale from 25 to 40 grammes. Mehu gives the low average of from 15 to 20 grammes.

Chemistry. Artificial Production of Urea.—To Wöhler (1828) is due the credit of having first artificially produced urea. To accomplish this, ammonium sulphate and potassium cyanate are dissolved in water in equivalent proportions, and the solution evaporated to dryness. The following reaction takes place:



* *Soc. de Biolog.*, 1870, pp. 75, 110, and *Gaz. Heb. de Med. et de Chir.*, 1870.

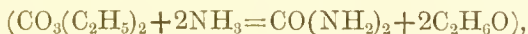
On boiling the solution of ammonium cyanate a molecular change ensues, the latter becoming converted into isomeric urea, thus :



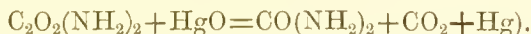
Potassium cyanate is easily made by the oxidation of potassium cyanide, and potassium cyanide is obtained by heating potassium ferrocyanide. Thus we have the preparation of urea on a large scale. Take 28 parts of $\text{K}_4\text{Fe}(\text{CN})_6$ and 14 parts of peroxide of manganese (MnO_2), previously well mixed and dried, and subject the mixture to slow combustion. Cyanate of potassium is thus obtained. The mass is treated with cold water, and subsequently decomposed by the addition of $20\frac{1}{2}$ parts of sulphate of ammonia. The resulting compound is evaporated to dryness in a water-bath. Urea, sulphate of potash, and an excess of ammonium sulphate remain. Absolute alcohol is then added, which dissolves out the urea, leaving the other constituents untouched. By filtering and evaporation the urea is deposited in beautiful crystals of considerable size. This is the best method of preparing urea ; but it may also be prepared by the action of oxychloride of carbon (phosgene gas) on ammonia,



of ethyl carbonate on ammonia,



and of mercuric oxide on oxamide



M. Bechamp has succeeded in producing urea by the oxidation with permanganate of potash of certain nitrogenous substances, such as gluten, and these observations are confirmed by Ritter. Urea is also produced by the action of peroxide of lead upon uric acid, and also by the action of alkalis upon alloxan and creatine.

Physical Properties.—From an aqueous solution urea crystallizes in the form of quadratic prisms with a rectangular terminal plane. From an alcoholic solution the planes are octahedral. It is of colourless appearance, and possesses a fresh odour like that of nitre. It is soluble in an equal weight of cold water, and in a much smaller quantity at a high temperature. It is easily soluble in alcohol, sparingly soluble in

ether, and quite insoluble in oil of turpentine. The crystals polarize with a faintish-blue colour. It possesses a somewhat bitter saline taste.

Urea constitutes a base which gives with most diluted acids well-defined crystalline salts. The principal salts of urea are :

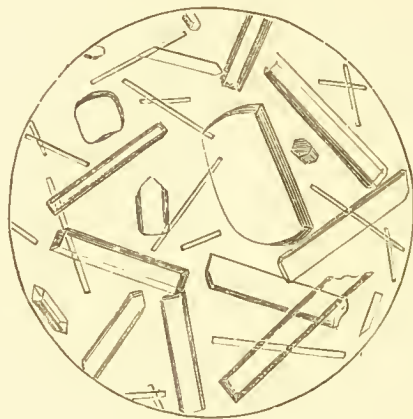


FIG. 8.—CRYSTALS OF UREA.

First, the *Nitrate*.—When nitric acid is added to a sufficiently concentrated solution of urea, it forms a crystalline precipitate of nitrate of urea— $\text{CO}(\text{NH}_2)_2 \cdot \text{HNO}_3$. The precipitate presents on microscopic examination a characteristic appearance. The crystals consist of large, yellow, hexagonal, and sometimes rhomboidal laminae, overlapping one another at the angles. If this salt be heated, it decomposes towards a temperature of 140° , giving off carbonic acid and protoxide of nitrogen. It is less soluble in water than urea, and is very little soluble in water impregnated with alcohol or nitric acid.

Second, *Oxalate of Urea*.—Oxalic acid added to a solution of urea acts similarly to nitric acid, and forms a precipitate of oxalate of urea— $(\text{CON}_2\text{H}_4)_2 \cdot \text{H}_2\text{C}_2\text{O}_4$. This salt crystallizes in prismatic scales. It is soluble in water, but less soluble than the nitrate. It can be dried up to a heat of 100° , but at 150° it decomposes. Oxalic acid has a greater affinity for urea than nitric acid has, so that when added to a solution of nitrate of urea a precipitate results which is not very soluble in water contain-

ing nitric acid. If chlorine gas is passed over fused urea, hydrochloric acid and nitrogen are evolved, and there remains a mixture of sal ammoniac and cyanuric acid :



But if a solution of urea be acted upon by a solution of chlorine gas or hypochlorous acid, the decomposition is totally different ; thus :



Hydrochloric acid, carbon dioxide, water, and nitrogen are thus formed. If, instead of free chlorine, an alkaline hypochlorite be used, the reaction is the same, only an alkaline chloride is formed, and the carbonic acid gas is not disengaged, but is retained by an excess of alkali. The more alkaline the medium, the more complete the reaction ; thus :

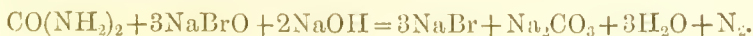


The carbonic acid gas is retained in the form of carbonate of soda, and only nitrogen is given off.



FIG. 9.—CRYSTALS OF NITRATE OF UREA.

Bromine and the alkaline hypobromites act in a similar manner, but more energetically. When a solution of urea is mixed with an excess of hypobromite of sodium, the former is rapidly decomposed, and evolves about 90 per cent. of its nitrogen :

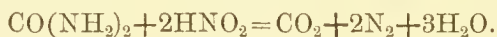


Heated with a solution of nitrate of silver, urea gives nitrate of ammonia and an insoluble cyanate of silver.

From the clinical aspect, it may be observed that with the addition of water urea is transformed into carbonate of ammonia. This reaction is facilitated by heat, but in course of time it takes place at the temperature of the air or of the body :



Nitrous acid or nitric acid charged with nitrous vapour very rapidly decomposes urea. This reaction has been interpreted in various manners, but according to the excellent observations of Boymond, the urea is decomposed, giving off equal volumes of carbonic acid and nitrogen ; thus with nitrous acid :



On mixing a solution of urea with mercuric nitrate, a white precipitate consisting of $\text{CO}(\text{NH}_2)_2$, 2HgO is obtained and nitric acid is set free. If the nitric acid be neutralized by the addition of an alkali or baryta water, the whole of the urea may be thus removed. It is on this reaction that Liebig's process for the estimation of urea is based. Phosphoric acid combines with urea to form a soluble phosphate. This salt has been described and studied by Lehmann, who found it in the urine of the pig. Sulphuric acid does not combine with urea ; neither does uric, hippuric, nor lactic acid.

Extraction and Preparation of Urea. — Urea may be extracted from the urine by various processes. The simplest is the method employed by Fourcroy and Vauquelin. This consists in evaporating the urine to a syrupy consistence, and in treating the residue with absolute alcohol. Urea as thus obtained is not, however, in a very pure form, and is difficult of crystallization. This process may be advantageously modified as follows : The alcoholic solution is evaporated, and the residue dissolved in water, filtered, and precipitated by nitric acid. The nitrate of urea thus obtained is collected, washed with water, and then decomposed by boiling with a solution of either bicarbonate of potash, carbonate of baryta, or carbonate of lead. The mixture is then evaporated and treated with concentrated alcohol, which dissolves the urea alone. This process has the following disadvantages : The

nitrate of urea is not entirely insoluble in water, and consequently there is always loss. Further, a certain proportion of nitro-muriatic acid is formed with the chlorides of the urine. A better method consists in precipitating the sulphates and phosphates of the urine by the addition of half its volume of a solution of baryta, filtering, and evaporating to dryness on a sand-bath. The residue is dissolved by absolute alcohol and evaporated. Two crystallizations may be requisite. The urine of the dog is much richer in urea than that of man, and may thus be more conveniently employed for purposes of investigation and experiment relating to urea.

Quantitative Analysis of Urea.—For few substances have more processes of volumetric analysis been employed than for urea. The following are the simplest and most reliable :

First, the process of decomposition by the hypochlorites (Léconte).

Second, the process of decomposition by means of nitric acid, on which are based the methods of Millon and Liebig.

Third, the process of decomposition by alkaline hypobromites.

Process of Léconte.—We have already seen (*vide* p. 49)

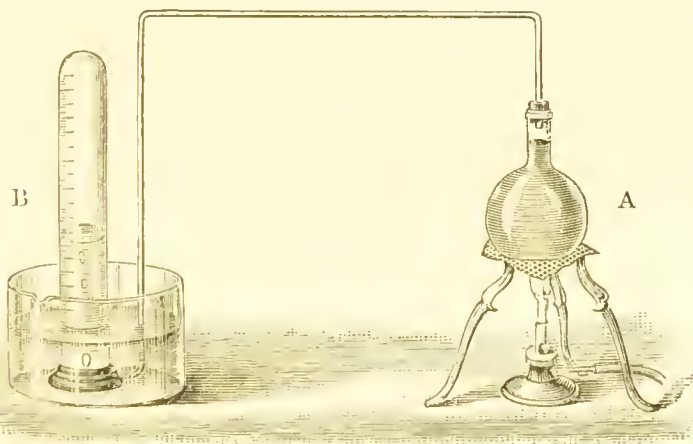


FIG. 10.

A, Decomposing flask ; B, Graduated tube for reception of nitrogen.

that urea is decomposed by chlorine into water, carbonic acid gas and nitrogen. This decomposition is similarly effected by

the hypochlorites, *e.g.*—the hypochlorite of soda. To prepare a solution for this purpose, dissolve 100 grammes of well-powdered 'ehloride of lime' in distilled or recently boiled and cold water; then dissolve in the filtered fluid 200 grammes of crystallized carbonate of soda reduced to powder; wash the resulting carbonate of lime, and make up to 2 litres. This solution should be preserved in a stoppered bottle.

The figure on page 51 represents the apparatus of Léeonte.

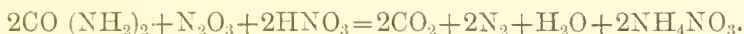
Proceed as follows: Take from 10 to 20 grammes of the urine, which introduce into a flask of a capacity of from 120 to 200 cubic centimetres. Fill the flask with the hypochlorite solution, and close the orifice by means of a cork through which a glass tube communicates with a graduated receiver full of water. Decomposition at once ensues, especially at the summer temperature. It is desirable, however, to apply heat by means of a spirit-lamp. The mixture is raised to the temperature of ebullition, and thus maintained until no more gas is evolved. The carbonic acid is retained in the flask, and nitrogen alone is collected in the receiver. On examining the formula of urea it will be found that theoretically 10 centigrammes (0.10) correspond to 37 cubic centimetres* of nitrogen, measured at a temperature of 0° and the normal pressure of 760 millimetres; but Léeonte has not been able to obtain more than 34 cubic centimetres by means of the hypochlorite of soda, and this figure (34) is adopted generally as the basis of calculation, though some other authorities maintain that the nitrogen given off is short of the absolute amount by 6 cubic centimetres.

If 34 c.c. of nitrogen be, then, equivalent to 10 centigrammes (0.10) of urea, a simple proportion sum will give the urea corresponding to the volume of nitrogen collected in the receiver. In order to obviate errors which may arise in the

* That one decigramme of urea will yield at a temperature of 0° and a pressure of 760 mill. 37 c.c. of nitrogen is evident from the following: 1 litre of nitrogen at 0° 760 m.m. = 1.2562 grms. Combining weight of urea = 60. Then, if 60 give 28 N by weight, what will 0.1 of urea give? ($60 : 0.1 :: 28 : x = 0.046$)—and, of course, 1 gm. of urea gives 0.46, or ten times as much as the decigramme. Now, 1 litre of nitrogen (1,000 c.c.) at 0° 760 m.m. = 1.2562 grms.; hence 1.2562 grms. : 0.46 gm. :: 1.000 : $x = 371.48$ c.c. nitrogen, and a decigramme 37.1 c.c.

course of this experiment from the presence of albumen and uric acid which may be partially decomposed by the chlorine, and thus evolve nitrogen, the urine ought previously to be purified as follows: To 20 grammes of urine, 3 grammes of subacetate of lead are added. The fluid is boiled, filtered, and the residue well washed; then 3 grammes of crystallized carbonate of soda are added. This fluid is in turn boiled, filtered and the residue washed. As the volume of the fluid has been augmented by the washings, the half, which represents 10 grammes of urine, is sufficient for the purpose of experiment.

Process of Millon.—This process is based on the decomposition of urea by a solution of nitrate of mercury charged with nitrous vapour. Thus:



The nitric acid is here employed in the form of a nitrate and nitrite of mercury, with an excess of nitric acid.

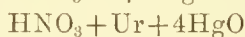
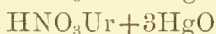
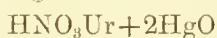
The reagent is prepared by dissolving 125 grammes of mercury in 168 grammes of nitric acid of a density of 1.44, and then diluting with twice the volume of water. Equal volumes of carbonic acid gas and nitrogen are given off. It is with the former alone that the process of Millon deals, and its amount is thus estimated: This gas is received in a tube containing a portion of caustic potash. Prior to the commencement of the experiment this tube is carefully weighed in a chemical balance. Subsequently the two gases pass over the caustic potash, but the carbonic acid gas alone is absorbed, and its weight is represented by the additional weight of the tube. This increased weight multiplied by 1.3636* gives the weight of urea contained in the specimen of urine operated on. Twenty grammes of urine should be introduced into a flask having a capacity of 200 cubic centimetres, and 50 cubic centimetres of the reagent of Millon should be employed.

Process of Liebig.—This process consists in the successive employment of a solution of baryta, which separates the sulphates and phosphates of the urine; a solution of nitrate of

* Combining weight of urea, 60; carbonic acid 44. $\therefore 60 \div 44 = 1.3636$; hence $\text{CO}_2 \times 1.3636 = \text{urea}$ in the 20 grammes of urine submitted to analysis.

mercury, which decomposes the urea ; and a solution of carbonate of soda, which indicates when the reaction is complete. The solution of nitrate of mercury is so prepared that 1 cubic centimetre of it corresponds to 1 centigramme (0.01) of urea. The mercuric nitrate decomposes the ehlorides into sodic nitrate, potassic nitrate and mercuric ehloride, and then combines with urea as under.

The preeipitate varies in composition, according to the degree of concentration of the fluid. The eomposition is represented by one of the three following formulæ :



In a solution of ehloride of sodium containing urea, a permanent precipitate of urea and oxide of mercury is not formed by a solution of the nitrate of mercury until the whole of the ehloride of sodium present has been decomposed and the nitrate thus converted into corrosive sublimate. Immediately on the ehloride of sodium being thus decomposed, the next drop of the solution of mercury throws down a permanent deposit of oxide of mercury and urea, which is insoluble in water.

Preparation of Liebig's Standard Solution.—Dissolve in strong nitric acid by aid of heat 77.2 grammes (1,196.6 grains) of dry oxide of mercury, so pure that on being heated on a platinum spatula no residue is left. Evaporate the solution to the consistence of a syrup, and then dilute up to 1,000 c.c. with distilled water. If any precipitate of basic salt form, add a few more drops of nitric acid. One c.c. of this solution is equal to 0.01 gramme (0.15 grain) of urea.

Baryta Solution.—Mix 1 part of cold saturated solution of nitrate of baryta with 2 parts of a cold saturated solution of caustic baryta, and reduce the mixture to half its strength by addition of an equal amount of distilled water.

Carbonate of Soda Solution.—A saturated solution, or about 1 gramme to 30 grammes of water, or 20 grains in 1 ounce of water. Dr. Harley has suggested for convenience the impregnating of white filter paper with the soda solution. The paper may be cut into strips of convenient size, and preserved in

a wide-mouthed stoppered bottle. A drop of the mixture to which a sufficient quantity of the nitrate of mercury has been added will stain this paper yellow (oxide of mercury).

Volumetric Analysis.—With a graduated pipette, take, for example, 40 c.c. of the urine to be examined, to which add 20 c.c. of the baryta solution. Stir the resulting mixture, and filter. Of this liquid take 15 c.c., which obviously correspond to 10 c.c. of urine, and add a few drops of nitric acid. Place these 15 c.c. of the mixture in a glass flask or glass beaker, and to this quantity add drop by drop the nitrate of mercury solution. The first drops produce no precipitate, as they form with the chlorides of the urine a soluble bichloride of mercury. The chlorides having thus entered into a new combination, the next addition of the nitrate of mercury solution causes a permanent precipitate of urea and oxide of mercury (1 equivalent of the former to 2 equivalents of the latter, or more, according to concentration). The quantity of the nitrate of mercury solution necessary for the saturation of the chlorides is carefully noted, and subtracted from the total required to be added until a drop of the solution gives a yellow colour in contact with a drop of the solution of the carbonate of soda. The yellow colour does not appear with the carbonate of soda solution until 1 volume of the solution of mercury, containing 77 parts of the oxide has been added to every 10 parts of urea—that is, 4 equivalents of the mercury to 1 of urea.*

If a bluish colour result with the soda solution, it is indicated that there is still free urea in the solution; a yellow colour (HgO —‘yellow wash’), that there is no free urea, but that there is an excess of the nitrate of mercury. Every cubic centimetre or every fractional part of the mercurial solution required for the second part of the experiment corresponds to a centigramme (0.01), or a corresponding fractional part of urea. The amount of urea in 10 c.c. being thus ascertained, it is a question of simple proportion to determine the daily excretion of urea. Thus, supposing that 1 c.c. of the solution was required to saturate the

* Theoretically, 100 parts of urea should require 720 parts of mercuric oxide, but the solution must be in excess to give the yellow colour.

chlorides, and that altogether 19 c.c. were used before the yellow coloration with the carbonate of soda solution was distinctly produced, then: $19 - 1 = 18 = 18$ centigrammes of urea (0.18). If the patient passed in 24 hours 1,850 c.c. of urine, then $10 : 1,850 :: 18 : x = 3,330$ centigrammes, or divided by 100 = 33.30 grammes.

By another process the chlorides may be separated from the urine by a standard solution of nitrate of silver, of which 1 c.c. corresponds to a centigramme of chloride of sodium. To prepare this solution, take of

Pure recrystallized nitrate of silver, 29.075 grammes :

Distilled water to 1,000 c.c.

Let 10 c.c. be taken, and the amount of chloride of sodium be determined by the silver solution, as by the method for determination of chlorides (*vide infra*). If it is found that 15 c.c. are required for this purpose, 0.15 centigrammes of sodium chloride are indicated. Then take 30 c.c. (containing 20 c.c. of urine) of the filtrate from the mixture of baryta fluid and urine, add a drop or two of nitric acid. Then if 10 require 15 of the silver solution, 20 must require 30. This should precipitate all the chlorides, which can now be removed by filtration.

Additional Corrections.—The mercury solution is graduated for a solution of urea which contains 2 per cent. of urea; hence 30 c.c. of the mercury solution are required for the complete precipitation of the urea in 15 c.c. of the urea solution. The mixture thus amounts to 45 c.c., in which there are 30 times 5.2 = 156 milligrammes of free oxide of mercury; every c.c., therefore, contains 3.47 milligrammes of oxide of mercury. If the 15 c.c. of urea solution contain 4 per cent. of urea, and we add 60 of the mercurial solution, a mixture amounting to 75 c.c. is produced, in which there are 312 milligrammes of the oxide of mercury (60×5.2), or 4.16 milligrammes in every c.c., being, therefore, an excess of 0.69 milligrammes ($4.16 - 3.47$) of oxide in every cubic centimetre above what is required to produce the final reaction with carbonate of soda. It is, therefore, clear that in experimenting on urine containing a larger amount of urea than 2 per cent., the urea will appear smaller than it really is. If the urine, as in the example given, contain 4 per cent., we should not add 60 c.c., but only 59.37 c.c. of the mercury solution.

To avoid this error, as soon as it is found that the percentage of urea is higher than that for which the mercurial solution is graduated, add for every additional c.c. of this solution required a half of water before testing with the carbonate of soda. If, for example, we have used 20 c.c. more than 30, we add 10 c.c. of water.

Modification when the Urea sinks below 1 per cent.—Should the quantity of the urea in the urine amount to only 1 per cent., we must add to 15 c.c. of urine, not 15 c.c. of the mercury solution, but 15.3 before the final test-point is reached. In consequence of this source of error, the amount of urea obtained is too great. In operating, then, on dilute urine, for every 5 c.c. of the mercury solution less than 30 which has been used, subtract 0.1 c.c. from the total amount employed. If, thus, for 15 c.c. of urine 25.0 c.c. of mercurial solution have been used, the real amount of urea, being 249 milligrammes, is expressed by 24.9 c.c. of mercurial solution.

The Urine contains Albumen.—In this case 50 c.c. of the urine are treated with 2 drops of strong acetic acid, and boiled to coagulate the albumen; the precipitate is allowed to settle, and 30 c.c. of the clear urine are mixed with 15 c.c. of the baryta solution, filtered, and treated as already described.

Liebig's process is thus a troublesome one, subject to errors requiring correction, and for simplicity and accuracy is of inferior value to one or other of the methods of determining the amount of urea by the alkaline hypobromites.

Volumetric Analysis of Urea by Hypobromite Process.—This process is based upon the fact that hypobromous acid decomposes urea into carbonic acid, water and nitrogen. The decomposition is as follows:



In this process the volume of nitrogen disengaged is the measure of urea.

The hypobromite solution is best prepared by dissolving 100 grammes ($3\frac{1}{2}$ ounces) of common caustic soda in 250 c.c. (9 ounces) of water, and when cold* adding 25 c.c. (7 drachms) of bromine.

* This is a necessary precaution, for unless the bromine be added to the soda solution when perfectly cold, the proper amount of nitrogen is not evolved when the experiment is conducted.

We have already seen (*vide* footnote, p. 52) that 1 gramme of urea yields 0.46 gramme of nitrogen by weight, and occupies a volume of 371.48 c.c.* at 0° and 760 m.m. It therefore follows that every cubic centimetre of nitrogen evolved, after a given quantity of urine is treated with the hypobromite solution,

represents a corresponding fractional part of a gramme of urea. Supposing the tube for the reception of the nitrogen to be graduated into cubic centimetres, and that 37.1 c.c. of nitrogen are evolved, it follows that this represents the tenth part of a gramme or 0.1 of urea. In this calculation the normal temperature and pressure are assumed. While 37.1 c.c. is absolutely the correct number, Léconte has never been able to obtain more than 34 c.c. of nitrogen from a decigramme of urea, and consequently 34 is usually adopted, especially in France, as the basis of calculation, and as being equivalent to 0.1 of urea at 0° and 760 m.m. Therefore, supposing 25 c.c. of nitrogen have been evolved from the urine experimented upon :

$$34 \text{ c.c.} : 25 :: 0.1 : x = .073 \text{ gramme of urea.}$$

It will be obvious that, to ascertain the quantity of urea passed in twenty-four hours, it will be necessary to know the volume of urine passed in twenty-four hours, and of the urine operated upon.

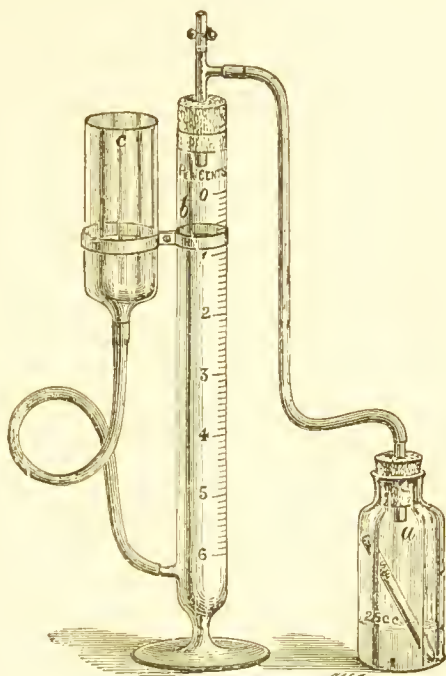
With a view to obviate the necessary corrections for temperature and pressure, Yvon has suggested the employment of this instrument. It consists of a glass tube of 40 centimetres in length. Towards its upper extremity it is traversed by a stop-cock, on either side of which the tube is graduated into tenths of a c.c. The instrument is inserted into a long narrow tube containing mercury, the stop-cock is opened, and the lower portion of it is thus filled with the mercury. The stop-cock is then closed and the instrument raised, and supported in the tube by means of



FIG. 11.—YVON'S UREOMETER.

* 371.48 c.c. N₂ : 1 c.c. N₂ :: 1 gr. : x = .002689 gr. urea.

FIG. 12. — GERRARD'S UREOMETER.* — This instrument consists of two tubes of unequal diameter and length, and connected by a piece of indiarubber tubing. The longer tube is filled with water, and is graduated for the estimation of the nitrogen received from a bottle also connected with it by indiarubber tubing, and in which the decomposition of the urine takes place by means of the hypobromite solution. The top of the measuring-tube is connected with a tube of indiarubber, which may be closed by a clamp.



Method of Using.—Pour into a test-tube 5 c.c. of the urine to be examined, and in the bottle (a) 25 c.c., or six fluid drachms, of sodium hypobromite solution. Place the tube carefully inside the bottle, as shown on the illustration, taking care to avoid any spilling of the contents. Fill the glass tube (b c) with water, so that the level reaches the zero line, taking care that when this is done the tube (c) contains only a little water by being placed high—it having to receive what is displaced from (c) by the nitrogen evolved. The clamp at the top of the long tube having been open to relieve pressure, this is now shut. Then connect the indiarubber tubing to the bottle, note that the water is exactly at zero, and upset the contents of the test-tube into the hypobromite solution. Nitrogen is evolved, which depresses the water in (b). When this ceases, lower the tube (c) until the level of the water in both tubes is equal. The tube is graduated in per cents. of urea, and cooling for five or ten minutes should be allowed to take place before the readings are taken. The solution of hypobromite of soda is made by dissolving 100 grammes of caustic soda in 250 c.c. of water, and when cold 22 c.c. of bromine are added. To obviate the disagreeable smell and dangers of the bromine vapour, the bromine can be obtained in hermetically-sealed glass tubes containing 2 c.c. One of these, placed in the large bottle with 25 c.c. of the soda solution, gives, when broken with a sharp shake, the exact quantity of hypobromite for one estimation of urea.

* Manufactured by Gibbs, Cuxson and Co., Wednesbury.

the arm of an ordinary stand. A kind of mercurial barometer is thus formed, into the chamber of which it is possible to introduce fluids without the admixture of air.

A standard solution of urea is first prepared, containing 1 centigramme (0.01) in 5 c.c., and this is measured in the upper

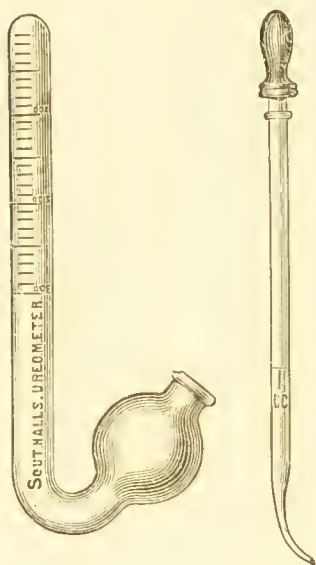


FIG. 13.—UREOMETER OF DOREMUS.*
—This simple instrument, originally designed by Dr. Charles Doremus, of New York, gives fairly accurate results.

Directions for Use.—Fill the vertical tube with a solution of hypobromite of sodium, by pouring the solution into the bulb until it is about half full. The apparatus should then be inclined horizontally until the entire tube is filled, about one-third being left in the bulb. Then restore the apparatus to the vertical position. Draw into the pipette 1 c.c. of the urine to be tested, pass the pipette into the apparatus, the point being placed immediately under the long arm. Compress the indiarubber cap slowly, and the gas which is liberated will thus pass up the long tube. It now collects in the upper part of the tube, and its volume being read off, indicates the amount of

uric acid from which it has been evolved. In cases where there is much uric acid, it is advisable to mix the urine with an equal amount of water before testing. In this case the result will be equal to one-half of that indicated on the scale. Each division of the instrument indicates .001 gramme of uric acid in 1 c.c. of urine. The percentage of uric acid is obtained by multiplying the result of the test by 100. To ascertain the total amount of uric acid voided in twenty-four hours, multiply the result by the number of c.c. of urine passed during that period. The instrument is also graduated to the English scale, each division indicating one grain of uric acid per fluid ounce of urine.

part of the tube, which is correspondingly graduated. Turning the stop-cock, the fluid descends into the lower portion of the tube, and the mercury descends correspondingly. The tube is then washed with a small quantity of a solution of caustic soda, which is mixed with the uric acid solution. Then from 5 to 6 c.c. of the hypobromite solution are introduced into the upper part of

* Manufactured by Southall Bros. and Barclay, Birmingham.

the tube, communication with the lower part being meantime shut off. By turning the stop-cock admixture of the fluids takes place, and reaction immediately commences, but no gas escapes, the pressure being more feeble inside than outside. To facilitate the admixture of the fluids, the thumb is placed on the lower portion of the tube and the instrument shaken. It is now re-

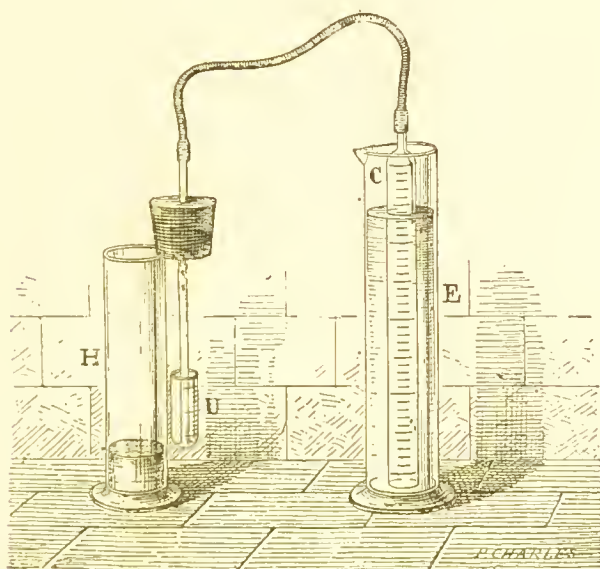


FIG. 14.—UREOMETER OF NOEL.

Mode of Using.—Fill the gauge E with water to within one or two centimetres below the zero mark of the graduated jar C. Then pour 15 c.c. of hypobromite solution into the tube H, and 2 c.c. of urine into the small graduated tube U, and about 2 c.c. of a saccharine solution. Establish the connections. Note that the level of the water in C is at zero. Incline the tube H. When the evolution of the gas has ceased read off the amount of nitrogen in the graduated tube C.

placed in the receiving-tube until such time as the evolution of all the nitrogen has taken place. The fluid then becomes of a yellow colour, and the operation is terminated. The instrument is now introduced into a tube full of water, when the more dense hypobromite solution flows out, leaving the gas, the amount of which is read off. This operation demonstrates that under

the conditions in which the experiment is conducted a given quantity of nitrogen is evolved. Under *the same* conditions a

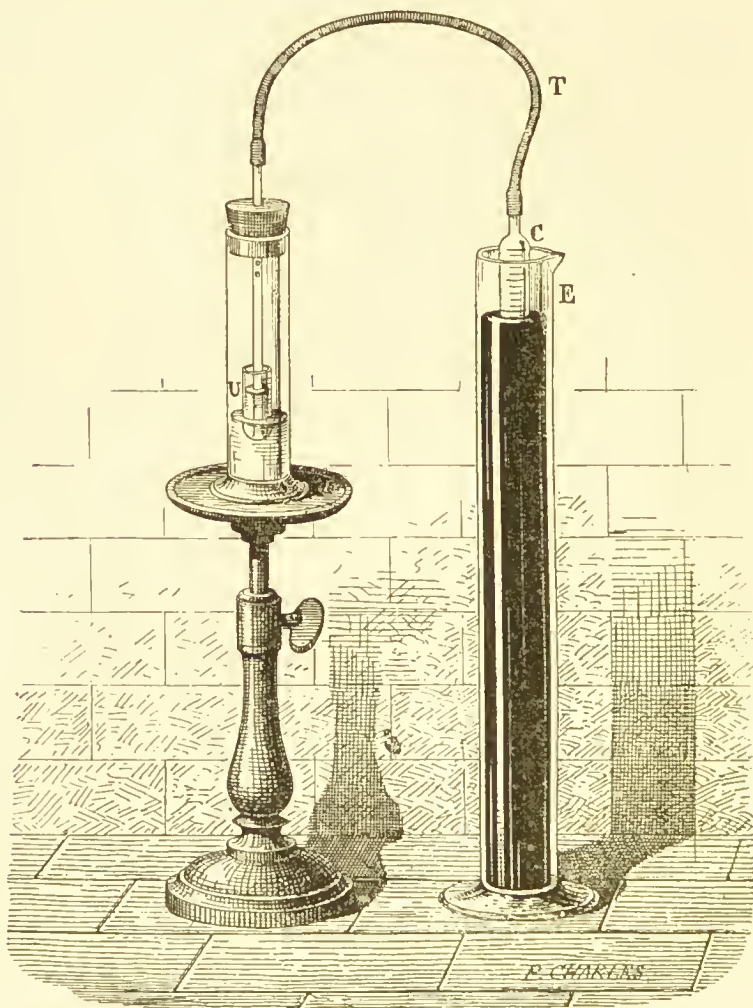


FIG. 15.—NOEL'S UREOMETER MODIFIED BY MERCIER.

In this apparatus the tube E is filled with mercury instead of water, so that any error from solubility of the nitrogen in the water is obviated. C. Tube for reception of the nitrogen divided into one-tenth c.c. ; E, Tube containing mercury ; T, Empty tube ; U, graduated urine-tube.

certain quantity of urine will give a relative amount of nitrogen gas. This comparison obviates the troublesome corrections as to temperature and pressure, the conditions being identical.

Therefore, if 1 centigramme of urea register 40 divisions of nitrogen or 4 c.c., and if a c.c. of urine give 88 divisions, then $40 : 88 :: 1 : x = 2$ centig. 2 mill. or 22 grammes per litre. Another source of error is further obviated by this process, viz., that arising from the fact that the hypobromite does not separate more than about 92 per cent. of the nitrogen, or about the same relative percentage between the theoretically correct number, 37 c.c., which a decigramme of urea ought to yield, and the 34 which practically Lécoute found it to yield.

Yvon used another ureometer, in which water takes the place of mercury, but as the principle is the same the process need not be here described.

Should the urine be found to be rich in urea, it may be diluted with twice or four times its volume of water, and the result multiplied accordingly.

Hypobromite of soda not only decomposes urea, but it likewise decomposes creatine, creatinine, uric acid, and the urates. In very exact analysis allowance must be made for this.

In order to eliminate the error in connection with the urates the following procedure should be adopted: Take 10 c.c. of urine, to which add 1 c.c. of a solution of subacetate of lead, then sufficient water to make up to 5 c.c., and filter. The urates are separated in the state of urate of lead, and the excess of lead in the solution does not prevent the decomposition of urea by the hypobromite of soda. The oxide of lead at first formed is dissolved in the alkaline fluid. The excess of subacetate of lead may be removed by carbonate of soda. For this purpose take 10 c.c. of urine in a graduated tube, and add a solution of carbonate of soda to make up to 50 c.c., shake, and filter. The urine is thus obtained free from lead.

Speaking generally, an augmentation of nitrogen to an extent of 4.5 per cent. may be allowed as arising from other sources than urea, and for clinical purposes it will be sufficient to subtract 4 per cent. from the amount of nitrogen obtained. Hence, if

1 centigramme of urea = say, 39 divisions of N,
 1 cubic centimetre of urine = 68 " "
 then

$39 : 68 :: 0.01 : x = 0.01743$ and per litre 17.43 grammes,
 then

$100 : 17.43 :: 4.5 : x = 0.78$ and $17.43 \text{ gr.} - 0.78 = 16.65 \text{ gr.}$,
 which represents very nearly the quantity of urea contained in
 a litre.

M. Mehu has made the very interesting and important observation that with urine containing glucose the hypobromite separates all the nitrogen contained in the urea. Hence, in conducting a volumetric analysis of urea, a watery solution of glucose may be used, instead of distilled water for diluting the urine.

Pathological Significance.—Urea represents the complete oxidation of the nitrogenous tissue of the body, and probably to some extent the transformation of nitrogenous constituents of food. It will follow that the amount of urea excreted will be in a direct ratio to the amount of tissue disintegration, and bear consequently a relative proportion to the combustion and temperature of the body. It is, therefore, notably increased in all febrile affections, in inflammations (such as pleurisy, pneumonia, meningitis), in eruptive fevers, in acute articular rheumatism, phthisis, etc.

In typhus fever and pneumonia from 50 to 60, or even 80, grammes (double that of health) may be excreted during the twenty-four hours. Increase of urea in febrile affections is of graver import when the ingestion of nitrogenous matter is reduced to a minimum. As the fever abates its excretion diminishes, and the diminution is maintained by the small amount of food usually taken, or the impaired functional activity of the digestive organs. With recurring appetite and strength the amount of urea again increases. In intermittent fever the urea is considerably augmented during the accession of the fever, and Ringer and Chalet have made the notable observation that the urea is in excess before the thermometer indicates an elevation of temperature. In typhoid fever Parkes found as much as 57 grammes (883.5 grains) in the urine of

twenty-four hours, and Vogel in one case the large amount of 78 grammes (1,209 grains). According to Sigmund,* the urea is augmented from the commencement of typhoid fever. In jaundice, according to Bouehardat, the urea is considerably increased. In two severe cases of this disease, on the third and fourth day he found from 59 to 133 grammes of urea in twenty-four hours' urine. In a case of chronic cerebritis, Dr. Harley found the proportion as high as 57.42 grammes (890 grains), and as the patient recovered it fell to 46.5 grammes (720.7 grains), and still later to 37.1 grammes (574 grains), in twenty-four hours. In a case of pyæmia, Vogel found 80 grammes (1,240 grains) of urea. In diabetes the amount is greatly increased. Dr. Harley has found as large an amount as 70 grammes (1,085 grains) in the twenty-four hours' urine of a gentleman of nearly fifty years of age. The same authority states that the average of twenty-nine analyses of diabetic urine yielded 47 grammes (723.5 grains)—a quantity greatly in excess of the normal amount. To some extent he believed this to be due to a rich animal diet.

In certain eruptive fevers the amount of urea is likewise augmented. Andral found in a case of urticaria with intense fever 30 per 1,000. In diabetes the amount of urea excreted per diem is augmented, though the percentage amount is diminished owing to the large quantity of urine secreted. Durante has observed a similar augmentation in varicella and erysipelas of the face.

The Amount of Urea is diminished, conversely, when tissue metamorphosis is retarded, and there is deficient oxidation of tissue; thus, in anæmia, with deficient red corpuscles, and consequently deficient oxidation, pulmonary emphysema, heart affections, cholera, uræmia, scorbutus, Addison's disease, etc. Thudichum states that the lowest amount of urea he has observed to be discharged by a patient during twenty-four hours was 5 grammes in 75 c.c. of pale, faintly alkaline urine. The patient was a lady suffering from anæmia, and an abdominal tumour caused by an accumulation of feces which had escaped through an ulcerated portion of the intestine.

* *Archiv. für Physiol. und Pathol. Ch. und Mic.* (Vienna, 1852)

According to Parkes, uric acid can always be found in the blood after all nitrogenous food is cut off; and this is held by some to be fatal to the theory of deficient oxidation as the cause of an excess of uric acid. It is quite possible that all the urea is not derived from the uric acid, and that under any circumstances

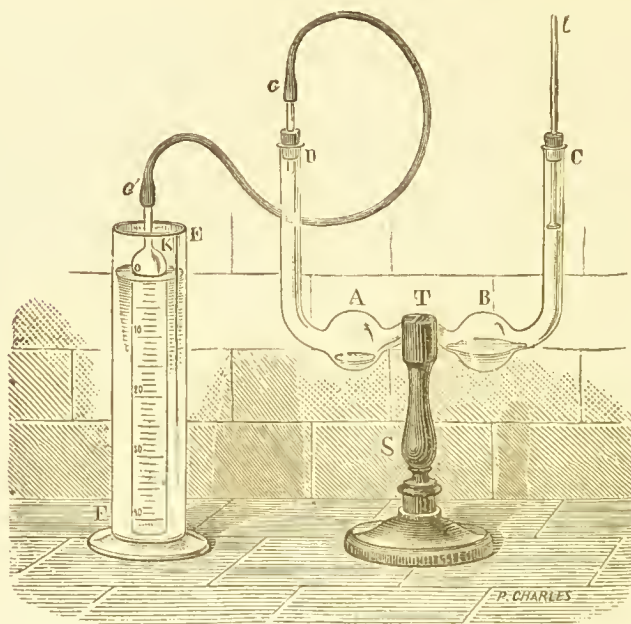


FIG. 16.—UREOMETER OF REGNARD.

E K, Receiver of gas; A, Bulb for the urine; B, Bulb for the reagent; *l*, Glass tube to diminish pressure.

Mode of Using.—Into the bulb A place 2 c.c. of the urine to be examined; into B about 10 c.c. of the hypobromite solution. Establish the connections. The level of the water should be identical in K and in the gauge E. This is accomplished by lowering or raising the glass tube (*l*). Incline the tube so that the two liquids may come in contact, when nitrogen is evolved and the result may be read off.

some of it must exist in the blood, and that thus no excess of oxygen would cause it entirely to disappear. Doubtless the other intermediate products, such as creatin and leucin and indican, contribute to the formation of urea. The fundamental principles of physiology point to oxidation as the process by which all the ultimate excreta are formed, and urea can be no exception.

In Addison's disease, while the amount of urea is diminished, the amount of indican is greatly augmented. Rosenstein,* in two cases of this nature, found that the urea diminished to from 20 to 12 grammes, while the normal quantity of indican increased tenfold. In a case of cancer of the liver, Hirne found the proportion of urea as low as from 6 to 7 grammes in 700 grammes of urine. In cholera, where the coldness of the body and general collapse indicate an arrest of the vital functions and diminished oxidation of tissue, there is a notable diminution of urea and other extractive matters of a lower form of oxidation. In a case of this description Desnos and Chalvet found but traces of urea with 4 per 1,000 extractive matter. In the blood of the same patient urea existed in the proportion of 3·6 per 1,000, and extractive matter 19 per 1,000. During the period of reaction the patient eliminated 700 grammes of urine in twenty-four hours, and the urea amounted to 28·8 per 1,000, and the extractive matter to 22. It is inferred that the collapse in this disease may be due to the retention in the blood, to some extent, of the urea and extractive matter, and that the conditions may have some etiological relationship with uræmia. The sweats which supervene in cholera during the period of reaction contain, as well as the urine, a large quantity of urea, which had been retained in the blood by the ischuria. On spontaneous evaporation of the cutaneous transudation, a white crystalline powder of urea forms. In dropsy the proportion of urea in the urine is notably diminished; but it is contained in the fluid effused into the various cavities and tissues of the body. In these cases, under the influence of diuretics, urea appears in large quantity in the urine. Urea is found in the fluid of hydrocele to the extent of 25·62 grm. per litre; and in dropsy the blood may be found to contain 0·365 grm. per litre, against 0·18 to 0·20, the normal quantity. In uræmia, that the diminution of urea is due to deficient oxidation† of tissue is shown by the greatly diminished temperature of the body. It is not clear, nor even probable, that the symptoms of uræmia are exclusively due to the retention of urea in the blood, but rather to other excremen-

* *Revue des Sciences Med.*, 1873, and *Virchow's Archiv.*, Bd. lvi.

† *Vide* 'Lectures on Bright's Disease,' by Author (Churchills).

titious elements which have not yet been isolated. Urea may be injected with impunity, in considerable doses, into the blood. In certain cases of albuminuria it is well known that there is a considerable diminution of urea. This seems to be due to arrested elimination, as well as to deficient formation. Into the latter question we cannot enter here, but on the former it may be remarked that this is characteristic of the 'small red granular kidney.'* In this condition we have large hyaline tube casts in the urine, which indicate that the convoluted tubes have been denuded of their epithelium, whose special function it is to separate the urinary solids; and hence we have a low specific gravity of urine (1010 to 1005), and urea and extractive matter accumulating in the blood.

Uræmia.—MM. Grehan and Quinquand have returned to the investigation of this subject by experimenting on animals. Subcutaneous injections of aqueous solutions of pure urea were employed in gradually increasing quantities on frogs, guinea-pigs, rabbits, pigeons and dogs. The result was constant for the different kinds of animals, and consisted in a more or less rapid death from tetanic convulsions, similar to those produced by strychnia. The most numerous experiments were performed on dogs. The toxic dose of urea in the blood was fixed with exactitude, and the influence of urea on muscular contractility was studied. Death always ensued when a dog received into its system 10 grammes of urea for every kilogramme of body weight. The proportion of urea in the blood, as estimated just before or after death, was 0·6 gramme for every 100 grammes of blood, and this relative proportion obtained in all other animals employed. In a case of azuria in a man, the proportion was ·410 per 100 grammes, and in another case of retention of urine ·278; in a case of interstitial nephritis, the patient suffering from uræmic dyspnœa, it was ·210, and in a case of uræmic coma ·215. Under the circumstances of the experiments all the tissues of the animals were impregnated with urea, so that 100 grammes of blood yielded 613 milligrammes of urea; 100 grammes of liver, 580 milligrammes; 100 grammes of cardiac tissue, 311 milligrammes; 100 grammes of spleen, 662 milligrammes. The

* *Vide* 'Lectures on Bright's Disease,' by Author (Churchill's).

observers always noticed that the urea injected under the skin was never completely absorbed, even at the time of death, though death might have been delayed for ten hours. They also found that uræmia does not increase nor diminish muscular contractility. The blood of dead animals, when submitted to distillation at a temperature of 40° C. *in vacuo*, furnished a liquid absolutely free from ammonia; the conclusion drawn from the experiment is that urea does not act as ammoniac carbonate. On the whole, it appears that leucamines, ptomaines and other extractives participate in the production of uræmia.

Medicinal Agents which influence the Excretion of Urea.

—The medicinal agents which influence the excretion of urea are divisible into two groups, viz, those which increase, and those which diminish, the amount of urea. These substances may be thus tabulated :

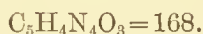
MEDICINAL AGENTS WHICH INCREASE THE AMOUNT OF UREA.	MEDICINAL AGENTS WHICH DIMINISH THE AMOUNT OF UREA.
Urea itself.	Digitalis.
Uric acid.	Alcohol. } †
Common salt.	Coffee. }
Phosphoric acid.	Tea. }
Squill.	Iodide of potassium and sodium.
Glycin.	Bromide of potassium.
Leucin.	Arsenic.
Theobromine.	Turpentine.
Colechicum.*	Nitrate of potash and soda.
Cubebs.	Alkaline carbonates.
Atropine.	Mercury.
Cantharides.	Antipyrin.
Vegetable acids.	Valerian.
Ferruginous preparations.	Sulphate of quinine.
Hypophosphite of soda.	Benzoic acid.
Chloride of potassium.	
Chloride of ammonium.	
Coca.	
Permanganate of potash.	
Large quantities of water.	
Oxygen.	

* *Vide* Author's 'Observations on Therapeutics and Disease' (Churchills).

† 'Aliments d'épargne.'

Therapeutic Indications.—If an excessive excretion of urea indicate a preternatural disintegration of nitrogenous tissue, and the system appear to suffer thereby, then a diet rich in nitrogen is indicated, such as animal soups, eggs, milk, etc., and one or other of the moderators of disintegration above tabulated. In health a farinaceous diet, such as arrowroot, sago, tapioca, etc., will diminish the amount of urea. Should it appear that too little urea is formed by the system, then exercise ought to be enjoined in order that more oxygen may be inhaled, and one of the group of exciters of metamorphosis administered, such as preparations of iron, common salt, permanganate of potash, etc.

URIC ACID.



Carbon	33·714
Hydrogen	1·191
Nitrogen	33·333
Oxygen	19·048
Water	10·714
			<hr/>
			100·000

Natural State—Extraction and Preparation of Uric Acid—Properties of Uric Acid—Urates—Acid Sodium Urate—Acid Potassium Urate—Acid Ammonium Urate—Acid Calcium Urate—Acid Magnesium Urate—Lithium Urate—Tests for Uric Acid—Quantitative Estimation of Uric Acid—Uric Acid in Albuminous Urine—Extraction of Uric Acid from Calculi and Sediments—Physiological Relations of Uric Acid—Pathology of Uric Acid—Therapeutic Indications.

Natural State.—After urea, uric acid is the most important normal element of the urine. It is found in all animals, even the lowest in the scale. Griffiths has found it in the green gland of the cray-fish; and MacMunn in the Malpighian tubes of insects and the nephridia of snails. Mettlebach found from 8 to 45 milligrammes of uric acid per 100 c.c. of urine in oxen. The statement is therefore inaccurate that it is absent in the urine of herbivorous animals, and is here replaced by hippuric acid. The urine of birds contains a large quantity of uric acid,

and that of serpents is almost entirely composed of pure uric acid. The urine of man contains a few decigrammes per diem. The blood contains it to a like amount, and here the proportion is largely augmented in cases of gout. It is likewise in all probability the *materies morbi* of rheumatism; and everything points to its being a product of suboxidation, as arising from an excessive protoid dietary, alcoholic and vinous indulgences, sedentary habits, and all such conditions as retard *cremæcausis*, either directly or indirectly. It is found either free or as urate of soda in the articular concretions of gout and in calculi. In conformity with what has been just remarked, it is reduced in amount* by active exercise in the open air, by the inhalation of oxygen, by lime-juice, alkaline carbonates, and vegetable acids (which are in the system converted into carbonates), by large doses of quinine, by common salt, by salicylates and benzoates of soda, salts of lithium, and notably by colchicum, by which it is converted into urea. It may be obtained for purposes of study from guano, or the excrement of serpents, from uric acid calculi, or from urine.

Extraction and Preparation.—Uric acid exists in the urine especially in the form of an alkaline urate. It is sometimes spontaneously deposited, in consequence of the reactions which accompany the cooling of urine; it is then more or less coloured. In order to extract uric acid from urine, about 20 c.c. of hydrochloric acid are added to a litre of urine, and the fluid is filtered. The urates are thus decomposed. The filtrate being allowed to stand for twenty-four hours, a precipitate of uric acid is found to have deposited on the bottom of the vessel. The precipitate is less coloured than that which spontaneously deposits in the urine; still, it presents the appearance of cayenne pepper. In order to obtain crystals in a state of purity, the crystals obtained as above are dissolved in sulphuric acid, and then precipitated with water, when small characteristic crystals of great whiteness are obtained. If the urine be of low specific gravity, it is well to concentrate it by evaporation before treatment with the hydrochloric acid.

* *Vide* 'Observations on Therapeutics and Disease,' by D. Campbell Black, M.D., etc. (J. and A. Churchill).

Properties of Uric Acid.—Thus prepared, uric acid is found to be a weak dibasic acid, which furnishes both acid and neutral salts. The neutral salts are more soluble than its acid salts. It presents the appearance of light scales, soft to the touch, and of a great variety of forms of crystallization. The rhombic form, with two obtuse angles, is the predominating crystalline form of uric acid. These crystals are often designated the 'lozenge' form of uric acid. A 'dumb-bell' form is also described, which frequently exists in sediments. It is well to note that oxalate and carbonate



FIG. 17.—TYPICAL FORMS OF URIC ACID CRYSTALS.

of lime present the same form of crystallization. Few substances present a greater variety of forms than uric acid. This acid has neither taste nor odour, and it does not redden litmus. It is very insoluble in water, requiring from 1,800 to 1,900 times its weight of cold water, and 1,400 to 1,500 of boiling water, to dissolve it. It is insoluble in alcohol and in ether. It dissolves easily in a solution of phosphate of soda, in fixed alkalies, in carbonates, phosphates, and borates of the fixed alkalies, but not in the corresponding ammoniacal salts. It dissolves with difficulty in ammonia. Sulphuric acid dissolves it without decomposition, and it may be precipitated therefrom by the addition of water. Nitric acid dissolves it, but decomposes it in so doing. A

potassic solution of uric acid reduces Fehling's solution, and may thus be confounded with glueose. Heated in a tube, uric acid decomposes into urea and cyanuric acid. It forms at the same time hydrocyanic acid and carbonate of ammonia. Boiled with acetate of lead, uric acid is decomposed into *carbonic acid*, *allantoin*, *urea*, and oxalic acid.

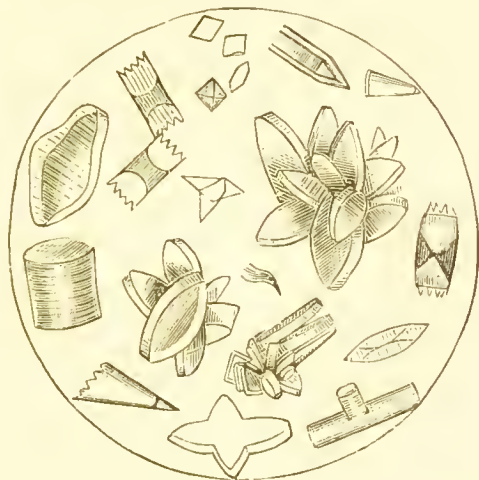
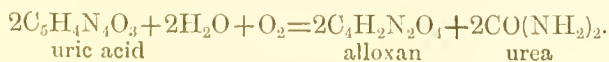


FIG. 18.—RARER FORMS OF URIC ACID CRYSTALS.

If one part of uric acid be treated with four parts of concentrated nitric acid, there is decomposition with effervescence, and the liquid solidifies. The following represents the decomposition which takes place :



Uric acid may be decomposed by carbonic acid, a fact which accounts for the presence of acid urates, and their deposition in the urine. Alloxan which originates as above is remarkable for the beautiful red coloration which it gives with ammoniacal vapour. This is due to the formation of iso-alloxanate of ammonia which characterizes uric acid (murexido reaction).* By the action of caustic potash this coloration changes to purple-

* From *murex*, a shell-fish of similar tint.

blue. All the urates give the murexide reaction. As with uric acid, the urates do not affect litmus.

Urates.—Uric acid forms with alkalies two series of salts—viz., the neutral urates and the acid urates, which are much more soluble than the free acid, and dissolve more easily in a hot than in a cold solution. Further, the neutral salts are more soluble than the acid salts; neutral urates of potassium and lithium are the most soluble, and acid urate of ammonia the least soluble. When hydrochloric or acetic acid is added to urine for the purpose of decomposing the urates, the uric acid separates in a crystalline form; and if the fluid is concentrated this takes place immediately, but if diluted a considerable interval will elapse before precipitation.

Uric acid, being very insoluble in water, does not exist normally in the urine as such, but is always found in combination in the form of acid sodium urate, acid potassium urate, acid ammonium urate, and, under rare circumstances, acid calcium urate.

Acid sodium urate ($C_5H_3NaN_4O_9$).—This constitutes the most common urate deposit, and presents a rose-colour when

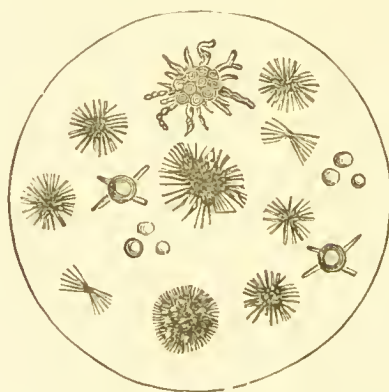


FIG. 19.—GROUPS OF ACICULAR CRYSTALS AND SPHERICAL MASSES OF SODIUM URATE.

it deposits in urine which has become cool. It is rendered soluble by the least elevation of temperature. Acid urate of sodium is soluble in about 1,200 parts of cold water, and in 125

parts of boiling water. Under the microscope, it presents the appearance of spherical granules, which are more frequently in clusters than singly. With nitric acid and ammonia, this salt gives the *murexide* reaction, and calcination leaves a residue of carbonate of soda.

Acid Potassium Urate ($C_5H_3KN_4O_3$).—This urate is almost always found in combination with that of soda, and is more soluble in water. One gramme dissolves in 800 parts of water at $15^\circ C.$, and in 75 of boiling water. It leaves on calcination a residue of carbonate of potash.

Acid Ammonium Urate ($C_5H_3(NH_4)N_4O_3$).—This urate is invariably found in urine which has become ammoniacal. It is very insoluble, 1 part requiring 1,600 parts of water for its solution. It leaves no residue on calcination. It is distinguishable from uric acid by the evolution of ammonia when heated with caustic soda. It presents the appearance of spheres, more or less voluminous, sometimes spiny. Two spheres are sometimes united by a peduncle, and thus present a dumb-bell appearance.

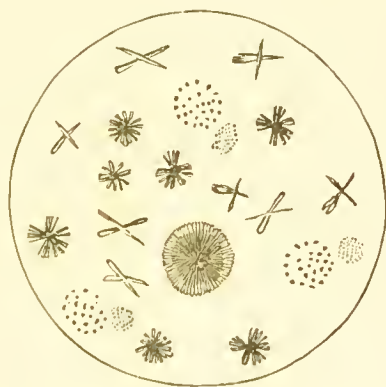


FIG. 20.—AMMONIUM URATE.

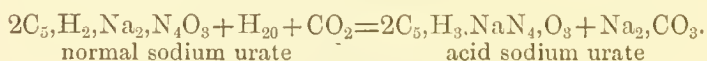
Acid Calcium Urate.—This form of urate is found much more rarely in the urine. It is frequently found in calculi. On calcination it leaves a residue of carbonate of lime. It is very insoluble in water. It effervesces with acids, and gives in solution the reaction of the salts of lime.

Acid Magnesium Urate is sometimes found in the urine

under similar circumstances. In solution it gives with acids the reactions of magnesium salts.

Urate of Lithium, the most soluble of all the urates, is sometimes found in urine. It dissolves in 116 times its weight of water at 39° C., and in 367 parts of water at 20° C. The salts of lithium are thus used therapeutically as eliminants of uric acid.*

In winter, owing to the cold, urates are found most frequently in the urine. When the urine is very acid, from containing a large proportion of acid phosphates, these appropriate from the neutral urates a portion of their base, and thus transform them into acid urates, which being less soluble than the neutral, are precipitated. Indeed, the acid phosphates may remove the whole of the base, and thus precipitate free uric acid. Hence the formation of deposits of urates and uric acid during the first period of the decomposition of urine on exposure to air. When heated, all the urates dissolve, and also on addition of caustic soda or potash, and when treated with acids they yield uric acid crystals. Corresponding to these acid urates, there are the normal urates of ammonium, sodium, potassium, calcium, and lithium. Being much more soluble than the acid urates, they remain in solution when precipitation of the latter takes place. The formation of carbonic acid in the urine may occasion the change from neutral to acid urates thus :



Tests for Uric Acid.—Uric acid is recognisable by its characteristic microscopic appearances. If but a small quantity of fluid be available, from 2 to 3 grammes are placed in a test-tube with two or three drops of a solution of glacial acetic acid, a piece of linen of from 3 to 4 c.c. in length is immersed in it, and the fluid is allowed to repose in a cool place for about twenty-four hours. The uric acid is found to

* Saturation of the urine with ammonium chloride precipitates all the urates. The murexide test can then be applied, and the quantity of uric acid in a given specimen of urine can thus be estimated by weighing.

have deposited on the linen, and the microscopic examination may then be made. It may also be separated by evaporating a small quantity of urine to dryness in a water-bath, any albumen having been previously removed. The residue is then treated with alcohol, to remove the urea and other constituents soluble therein. Then the fluid is treated with weak hydrochloric acid to remove the salts, and the uric acid alone remains. The result of microscopic examination may be confirmed by chemical tests. Thus, in a small porcelain capsule a little of the sediment, or of the residue obtained as above, is placed, and moistened with a drop or two of nitric acid. The uric acid dissolves with effervescence, giving off reddish vapours. Moderate heat is then applied to volatilize the excess of acid, a reddish-coloured residue being the result, and one or two drops of a solution of ammonia added (1 gramme of ammonia to 9 grammes of water), when a purple coloration is obtained, which constitutes the *murxide test* (ammonium purpurate— $C_8H_4(NH_4)N_5O_6$). The same result is obtained by exposure to ammoniacal vapour. The addition of caustic potash or soda causes a violet-blue coloration.

According to Magnier de la Source, the reaction may be better accomplished in the following manner: Instead of employing nitric acid, a few drops of bromine water (5 or 6 drops of bromine to 100 c.c. of water) are added to the residue operated on, and the whole evaporated on a water-bath. The ammonia is then added, when a purple coloration, which on the addition of potash passes into a violet-blue, is the result. These tests are of extreme delicacy.

Schiff's Test.—A little of the residue is dissolved in sodium carbonate, and a drop of the solution is then placed on a piece of filter-paper, previously moistened with a solution of nitrate of silver, when a brownish stain is produced, due to deposition of metallic silver.

Rosenberg's Reaction.—If an equal volume of a solution of phosphotungstic acid be added to urine, with a drop of caustic potash, soda, or ammonia, a blue coloration, due to the presence of uric acid, results (*Pharm. Centralhalle*, xxxi., 1890).

Reaction of Dietrich.—If a little uric acid solution be added to

an iodized solution of hypochlorite of sodium a rose coloration is produced, which disappears if the sodium solution be in excess.

If an alkaline solution of uric acid or of urates be heated with the liquor of Barriswell,* a white precipitate of urate of copper and a red precipitate of urate of copper (cuprosum) result. This precipitate must not be confounded with the precipitate similarly caused by glueose.

If a solution of uric acid in caustic soda be boiled with a small amount of Fehling's reagent, a grayish precipitate of urate of cuprous oxide is obtained. Should the copper salt be in excess, a red cuprous oxide is the result.

Quantitative Estimation of Uric Acid.—Empirically, a rough estimate of the amount of uric acid in urine may be obtained by multiplying the two last figures of the density by 2, when the result would express in centigrammes the quantity of uric acid per litre. While the process is somewhat troublesome, weighing alone gives the most accurate quantitative results. For this purpose the acid is precipitated as above by hydrochloric acid, and collected after sufficient repose in a cool place. One hundred c.c. of filtered urine (any albumen having been removed) are placed in a porcelain capsule, and 3 to 4 per cent. of hydrochloric acid added; after from twenty-four to thirty hours' repose the crystals are collected on a filter, whose tare has been obtained. The uric acid is washed with distilled water, which process is continued until the wash-water is no longer acid. The uric acid is then to be washed with alcohol to remove hippuric acid and any accidental colouring matters. It is then dried at a temperature of 100° C. until it ceases to lose weight; from the final weighing the weight of the filter is deducted, the result being the weight of uric acid. Uric acid is not absolutely insoluble in water, nor in water acidulated with hydrochloric acid. Hence to obtain perfect accuracy of result, an allowance must be made for the portion dissolved by adding 0.0045 gram. for each c.c. of water employed in washing.

Haycraft's Method.—This process requires (1) a centinormal

* Cupro-potassic liquor.

solution of sulphocyanide of potassium, to obtain which 8 grammes of this salt are dissolved in a litre of water: 1 c.c. $\frac{N}{100} = 0.00168$ of uric acid; (2) a decinormal solution of nitrate of silver; (3) a saturated solution of iron alum; (4) a 20 to 30 per cent. solution of nitric acid; (5) a solution of ammonia; and (6) an ammoniacal solution of nitrate of silver, to obtain which 5 grammes of nitrate of silver are dissolved in 100 c.c. of water, a sufficiency of ammonia being added to produce a limpid solution.

Process.—To 25 c.c. of urine containing no albumen add 1 gramme of sodium bicarbonate, and from 2 to 3 c.c. of the ammoniacal solution; then add from 1 to 2 c.c. of the silver solution, in order to precipitate the uric acid as urate of silver. Wash the precipitate with distilled water in order to remove the excess of the soluble silver salt; dissolve the precipitate in a few c.c. of nitric acid solution, and precipitate the silver with the solution of sulphocyanide of potassium, the iron alum serving as an indicator, the number of c.c. of $\frac{N}{100}$ of the sulphocyanide solution, multiplied by 0.00168 gramme, indicating the quantity of uric acid.

This process is based on the precipitation of uric acid in a state of urate of silver, insoluble in ammonia and soluble in nitric acid. Haycraft attributes the irregularity of the composition of urate of silver, as indicated by Salkowski, in part to the precipitation of ammonio-phosphate of magnesium, and in part to the reduction of the silver, which varies with time and temperature.

Salkowski-Ludwig Method.—If an ammoniacal solution of nitrate of silver be added to a solution of uric acid, to which has been previously added an ammoniacal mixture of chloride of magnesium and of chloride of ammonium, the uric acid is precipitated as a magnesio-silver salt. This is collected, washed, and decomposed by either sodium or potassium hydrosulphide. When the uric acid again passes into solution as a urate of the alkali. When an excess of hydrochloric acid is added to this solution, the urate is decomposed; the uric acid is separated out, and may thus be collected and weighed.

Process of Bayrac.—Of the nitrogenous compounds of the

urine, urea, uric acid, and creatinine are alone decomposed by hypobromite of soda, evolving their nitrogen incompletely in the cold; and completely on being heated. The other nitrogenous constituents exist in urine in so small an amount as not to merit consideration. The principle of this process consists in separating the uric acid from the two other nitrogenous constituents by means of alcohol, and in acting on the isolated principle, by means of a concentrated solution of hypobromite of soda, at a temperature of from 90° to 100° C. Fifty c.c. of urine are concentrated on a water-bath, the uric acid precipitated by 5 c.c. or 10 c.c. of dilute hydrochloric acid, and washed with alcohol. This removes the creatinine, and the urea, leaving the uric acid; the acid is then dissolved on a water-bath by 20 drops of caustic soda, and treated with 15 c.c. of a concentrated solution of hypobromite of soda, at a temperature of from 90° to 100° C. (*Journal de Pharmacie et de Chimie*, xxi., 1890, p. 611).

Of other processes for the quantitative analysis of uric acid may be mentioned those of Arth* and Butte.†

Uric Acid in Albuminous Urine.—When the urine contains albumen, as hydrochloric acid precipitates this body, it is necessary to employ a 6 per cent. solution of phosphoric acid, or an equal volume of glacial acetic acid, which precipitates the uric acid to the exclusion of the albumen. In the case of a more or less considerable quantity of urine, the albumen may be coagulated by heat, and thus separated by pouring on a filter. The filtrate, plus the water employed to wash the albumen coagulum, being mixed and concentrated if necessary, the amount of uric acid may be determined in the ordinary manner.

If a precipitate of urate or of free acid has already formed in a vessel, it must be vigorously agitated, and be rapidly poured into another vessel, a few drops of caustic soda being added to cause solution, and then the whole is filtered; the filtered liquid, being exactly measured, is employed for the determination of the uric acid and the albumen. Instead of the soda solution

* *Comp. Rend. de l'Acad. des Sciences*, February 17, 1890.

† *Répertoire de Pharmacie*, 1890, p. 38.

a gentle heat, not sufficient to coagulate the albumen, may be employed to dissolve the urate deposit.

Extraction of Uric Acid from Calculi and Sediments.—

The calculi or sediments, finely pulverized, are dissolved in caustic potash, and after filtration the solution is acidified with hydrochloric acid. The uric acid is again dissolved in caustic potash and reprecipitated by the acid, until the product obtained be sufficiently pure. Instead of treating the potash solution with hydrochloric acid, M. Mehu advises the passing of a current of carbonic acid gas through the solution, whereby the free alkali becomes a carbonate, while the uric acid is deposited in the condition of a urate of potash. This deposit may be then collected, carefully washed, and decomposed by hydrochloric acid.

Physiological Relations of Uric Acid.—In common with urea, uric acid results from the metamorphosis of proteid elements in the economy; but it is not an ultimate product of combustion, for when introduced into the system it undergoes further combustion, forming urea. The quantity of uric acid eliminated in twenty-four hours is much less than that of urea, varying from 0·30 gramme to 0·80 gramme, or an average of 0·55 gramme, or about one-tenth of the solid matters of the urine. This average varies according to circumstances. A proteid diet augments the amount of uric acid, while a non-nitrogenous dietary causes a diminution. A diminution also appears after indulgence in copious draughts. The greater portion of the uric acid is contained in the urine in the form of an alkaline urate; sometimes the urine contains uric acid in a free state, which separates either after emission of the urine, owing to acid fermentation, or in the bladder. In all quantitative analyses of uric acid, the entire urine of twenty-four hours must be operated upon, owing to the feeble solubility of the acid. When the proportion of uric acid in the body may be quite normal, a very little diminution in the urinary secretion may suffice to cause an abundant precipitation.

Pathology of Uric Acid.—Uric acid is excreted in augmented amount in all febrile affections, accompanied by embarrassment of respiration, such as pleurisy, pericarditis, capillary bronchitis,

chronic emphysema, etc., there being obviously in these circumstances a deficiency of oxidation. The same thing obtains in leucocythæmia, pernicious anæmia, and in the constitutional condition termed the *uric acid diathesis*, the cause being evidently the same. The blood being poor in iron, the organic combustion is less perfect. In the uric acid diathesis the acid separates in the urinary passages, and is eliminated with the urine in the form of little reddish particles, known as *uric acid gravel*. In cases of articular rheumatism,* the amount of uric acid is augmented during the period of greatest intensity of the fever, and diminishes during its decline. Its amount is also diminished in chronic rheumatism. It forms concretions of urate of soda in the joints in gout; and before the attack its excretion is very feeble, while after the attack it augments, and finally diminishes. In chronic gout a diminution is observed. In cases of obesity and diabetes there is a diminution of uric acid. In a certain form of glycosuria, described by Bouchard as *glycopolymuric diabetes*, there is, on the contrary, a considerable augmentation of this body, amounting to as much as 3 grammes per diem, during which period the sugar diminishes in quantity or totally disappears. In cases of interstitial nephritis, where there is desquamation of the cells of the convoluted tubes, there is, for obvious reasons, a diminished amount of uric acid. The same obtains in grave cases of scarlet fever. In cases of typhoid fever the appearance of uric acid or of urates in the urine has been held as indicating a period of crisis. According to Bouchard, in cases of lead-poisoning the proportion of uric acid is diminished to about a half. Haig maintains that its presence in the blood augments vascular tension.

Therapeutic Indications.—If an excess of uric acid represent an imperfect oxidation of proteids in the body, and the full oxidation be represented by urica, then the dietary should be regulated accordingly, and the medicinal agents administered should be such as stimulate and augment eremacausis. Nitrogenous diet should be restricted, and vegetable and farinaceous diet be enjoined. Sulphate of quinine diminishes uric acid, as likewise bicarbonates, alkaline carbonates, and vegetable acids (which are

* *Vide* Author's 'Observations on Therapeutics and Disease.'

converted in the system into carbonates), and all of which act as energetic oxidizing agents. Common salt, sulphate, carbonate, salicylate, and benzoate of soda, and inhalations of oxygen* act in a similar manner. The administration of colehium is indicated, for there is sufficient scientific testimony to its augmenting the amount of urea by diminishing and transforming uric acid, which it appears to effect in the liver. The salts of lithium cause the speedy disappearance of uric acid,† and piperazine is said to possess a similar property.

HIPPURIC ACID.

Hippuric Acid ($C_9H_9NO_3$) is found especially in the urine of the herbivora, as the horse, the ox, &c. In the urine of the carnivora, and especially in that of man, it exists in but a very minute quantity. It occurs here, however, after the ingestion of certain vegetables, such as asparagus, plums, whortle-berries, brambles, and generally a purely vegetable diet, and from the use of benzoic acid, cinnamic acid, essence of bitter almonds, quinine, and analogous bodies. Its presence has been demonstrated in the urine of new-born infants for some days after birth. Some authors maintain its existence in the blood, in the suprarenal capsules,

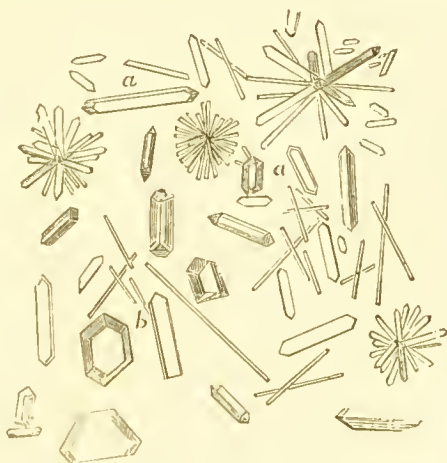


FIG. 21.—HIPPURIC ACID.
(a) Rhombic prism; (b) needle form.

* Vide Author's 'Observations on Therapeutics and Disease.'

† Lithium carbonate dissolves in 200 parts of boiling water. With an equal weight of uric acid half that quantity of water will suffice even at the temperature of the body. The uric acid eliminates carbonic acid from the carbonate. Salts of lithium are consequently prescribed in cases of gout and the *uric acid diathesis*.

and the sweat, but this is doubtful. In the urine, hippuric acid is found as a hippurate of soda or potash (urine of the horse). It is not probable that it exists in a free state in the urine in even the feeblest proportion. Hippuric acid is colourless, odourless, and of a slightly bitter taste; it crystallizes in the form of rhomboidal prisms, with pyramidal ends, and sometimes in the form of fine needles. These crystals are frequently arranged in groups, and present a semi-transparent or milky appearance. They dissolve in 600 parts of cold water, and in a much smaller amount of boiling water. They are easily soluble in alcohol and insoluble in petroleum-ether, and may be thus separated from benzoic acid, which is soluble in this reagent. Solutions of hippuric acid strongly redden litmus paper.

Hippuric acid, when feebly heated in a test-tube, is transformed into an oily fluid, which solidifies on cooling; at a higher temperature the mass becomes red, and evolves benzoic acid and an agreeable odour of hay, ultimately becoming of the odour of hydrocyanic acid. When it is evaporated with concentrated nitric acid it evolves an odour of nitro-benzene. Hippuric acid is monobasic and forms salts, with the exception of its iron salts, which are freely soluble in water. When boiled with concentrated mineral acids, or heated for a long time with water at a temperature of 170° to 180° C., it is resolved into benzoic acid and glycoll. When it undergoes the alkaline fermentation under the influence of the *Micrococcus ureæ*, the same change ensues. Hence it is not found in putrid urine, where its place is taken by benzoic acid, which is one of the products of the change. It is formed in the body by the union of benzoic acid with glycin (glycoll).

Extraction.—To extract hippuric acid, the following is the most convenient process: Concentrate on a water-bath to an eighth of its volume a portion of the fresh urine of a horse; add hydrochloric acid, and after a period of repose the hippuric acid separates in fine needles. It is preferable, however, to saturate the fresh urine with lime-water, which transforms the hippuric into a salt of lime; the fluid is then filtered, evaporated to a syrupy consistence, and decomposed by hydrochloric acid. Cazeneuve recommends that a litre of urine be evaporated to a

tenth of its volume, or 100 grammes, and then mixed with 200 grammes of 'plaster' (CaCO_3) and 20 grammes of alum, and dried on a water-bath. The alum, whose reaction is acid, decomposes the carbonates and sets the hippuric acid at liberty. The mixture is then placed in a digester and acted upon by boiling ether, which dissolves out the benzoic acid and fatty matter, and leaves crystals of hippuric acid of great brilliancy. It is easily traced in the urine after the administration of benzoic acid.

Tests and Quantitative Analysis.—Submit the crystals obtained as above to microscopic examination, and in confirmation effect the above-mentioned reactions. Its quantity can be determined by weighing the crystals.

Meissner advises that a kilogramme of fresh urine be operated on; add to it a solution of baryta until a precipitate is obtained, filter, and to the filtered fluid add drop by drop dilute sulphuric acid, so as to leave no trace of baryta. Care must be taken not to add an excess of sulphuric acid. Filter anew, and exactly neutralize with hydrochloric acid; evaporate on a water-bath to the consistency of a thick syrup; pour into a wide-mouthed vessel containing 200 c.c. of absolute alcohol. The succinates and the chloride of sodium precipitate, and the hippuric acid remains in solution. After agitation and prolonged repose, re-filter, and evaporate the alcohol on a water-bath; the residue is again placed in a wide-mouthed bottle, and treated with hydrochloric acid and about 125 grammes of slightly alcoholized sulphuric ether. On being agitated the hippuric acid is set free, dissolving in the ether, and may be precipitated by evaporation, and then dried and weighed.*

Physiology and Pathology.—Hippuric acid is found in normal human urine in very small quantities—0.30 gramme to 1 gramme in twenty-four hours. Its amount varies according to alimentation. After the ingestion of benzoic acid its amount is augmented; on a flesh dietary, even, it may appear in the urine, being derived in this case from the decomposition of proteids. The change from benzoic acid into hippuric seems to be effected

* One or two drops of a neutral solution of ferric chloride give a light red precipitate with hippuric acid.

by the cells of the convoluted tubes.* According to Salomon, after the excision of the kidneys in rabbits and injection of benzoic acid into the blood, hippuric acid could be detected in the blood, muscles, and liver; on the other hand, in diseases of the kidneys, it was found that benzoic acid was no longer capable of being transformed into hippuric acid. It is stated that even in excised kidneys the injection of benzoic acid is followed by the appearance of hippuric acid in the blood which flows from the organ. It is said to be augmented in the urine in diabetes and chorea.

CREATINE AND CREATININE.

Creatine ($C_4H_9N_3O_2$)† exists normally in muscular tissue, both striated and unstriated, to the extent of 2 per cent. The urine does not normally contain creatine, that which is found in it originating in the transformation of *creatinine*. The physiological rôle of creatine is undetermined. It does not seem to act as an aliment, inasmuch as it too speedily transforms into excrementitious bodies, such as urea, creatinine, and sarcosine ($C_3H_7NO_2$).

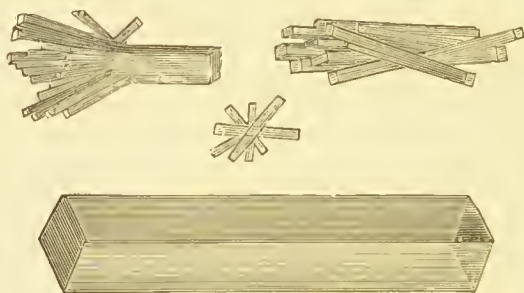


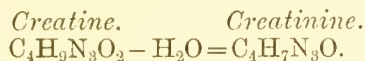
FIG. 22.—CREATINE.

Creatine occurs as rhomboidal, colourless, and very brilliant prisms. It has a sharp, bitter taste, and dissolves in 75 parts of cold water, in 9410 parts of alcohol, and not at all in ether. The solution has no action on vegetable colours, and evaporation transforms the creatine into creatinine. This transformation

* *Vide* Beaunis's 'Physiology,' vol. i., p. 282.

† Methyl-guanidine acetic acid.

takes place rapidly in presence of concentrated acids, the result being the loss of two molecules of water :



With chloride of zinc, concentrated solutions give a crystalline precipitate of chloride of zinc and creatine. When boiled with caustic alkalies and water, creatine is transformed into urea and sarcosine, the former being in great part in turn decomposed into carbonate of ammonia. Dilute mineral acids dissolve creatine without decomposing it, and crystallizable salts are thus obtained. At the boiling-point it reduces the salts of mercury.

Extraction.—A portion of beef is minced and treated with one and a half its volume of alcohol at 90° C. ; it is then heated in a closed vessel on a water-bath. The same process is repeated, with a fresh portion of alcohol. The two alcoholic liquids are united, the fluid passed through linen, and the alcohol removed by distillation. The residue of the distillation is then diluted with water and treated with an excess of acetate of lead, and the precipitate which forms is removed by filtration and rejected. The excess of lead is removed by a current of sulphuretted hydrogen ; and after a second filtration, to separate the sulphide of lead, the fluid is evaporated in a water-bath to the consistency of a syrup. After some hours' standing in a cool place crystals of creatine are deposited. These may be purified by boiling in water with animal charcoal, filtrated, and crystallized. Instead of minced beef, 'Liebig's Extract' may be used, and the subsequent processes followed out as above. The quantitative analysis of creatine is made by weighing.

By prolonged boiling, creatine reduces Fehling's solution without any separation of cuprous oxide ; and on boiling with an alkaline mercuric oxide, a transient red colour is obtained, and ultimately there is a separation of metallic mercury.

Creatinine ($\text{C}_4\text{H}_7\text{N}_3\text{O}$).—This substance, discovered by Liebig in the urine, is a powerful non-volatile, animal base. It displaces ammonia from its salts. It forms prismatic, colourless, and very brilliant crystals ; soluble in 11 parts of cold water, 100 parts of absolute alcohol, being still more soluble in

these *media* when heated. Creatinine is but very sparingly soluble in ether. Its solutions are feebly alkaline; with mineral acids it forms crystals, which are freely soluble. When concentrated urine is treated with ehloride of zinc, two double ehlorides are formed—viz., a ehloride of zinc and creatine, and a ehloride of zinc and creatinine. Creatinine exists in the urine to the extent of 0·5 to 4·9 grammes per diem.

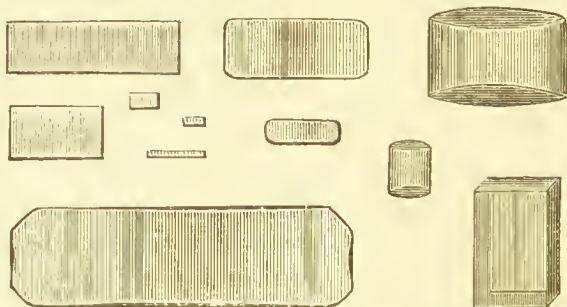


FIG. 23.—CREATININE.

The ehloride of zinc and creatinine— $(C_4H_7N_3O), 2ZnCl_2$ —dissolves sparingly in cold water; it is more easily soluble in boiling water, and is insoluble in aleohol. The creatinine may be thus isolated. Nitrate of silver, bichloride, and nitrate of binoxide of mercury preeipitate solutions of creatinine. In alkaline solutions creatinine is slowly transformed into creatine; heat favours this ehange, which spontaneously takes place if a solution of creatinine be abandoned for a month or two.



FIG. 24.—DOUBLE CHLORIDE OF ZINC AND CREATININE.

Extraction.—In order to extract creatinine from the urine, 300 c.e. of urine are preeipitated with a mixture of lime-water and of ehloride of ealcium; if the urine be albuminous, the albumen must be removed by coagulation, and if it contain sugar, this must be destroyed by fermentation. The liquid is to be concentrated to a syrupy consistence, and from 40 to 50 c.c.

of alcohol are to be added at a temperature of 95°C . After standing for eight hours, the liquid is filtered and washed with a little alcohol. If the solution occupy a volume of more than 60 c.c., it is to be concentrated in a water-bath; on cooling, one-half a c.c. of a saturated solution of chloride of zinc is to be added, the fluid agitated, and allowed to stand for two or three days, at the end of which time creatinine is deposited on the walls of the vessel. In order to isolate the creatinine, the double salt is to be dissolved in boiling water, and then boiled during a quarter of an hour with hydrated oxide of lead. Decolorize the solution with animal charcoal and evaporate to dryness. The residue consists of a mixture of creatine and creatinine. Treated with alcohol, the creatinine is dissolved and the creatine left behind. On evaporating the alcoholic solution, the creatinine deposits in beautiful crystals; and the creatine may be obtained by crystallizing from boiling water, or instead of extracting the creatinine from the urine, it may be obtained by the transformation of creatine. For this purpose the creatine is to be heated for about an hour with hydrochloric acid on a water-bath; evaporate so as to remove as much as possible of the free acid, when chlorhydrate of creatinine crystallizes. Finally, these crystals are dissolved in about three or four times their weight of water, and decomposed by boiling with oxide of lead; chloride of lead is formed, and the creatinine is set free.

Tests.—The presence of creatinine is demonstrated by Weyl's test. Mix a few drops of a dilute solution of nitro-prussiate of soda and a few drops of diluted caustic soda with the urine; the liquid assumes a beautiful ruby colour, which soon passes to yellow. If after decoloration a little acetic acid be added, a greenish-blue colour is produced. The presence of albumen in the urine does not prevent this reaction, and it is not caused by any other of the constituents of the urine. If the urine be of too deep a colour, this reaction fails. In this case it is necessary to isolate the creatinine in a pure state by the formation of a chloride of zinc and creatinine as above, and then submit the solution of one or other of these to the action of the nitro-prussiate of soda and the solution of soda. Creatinine may be recognised in the urine by its crystalline form. Creatinine

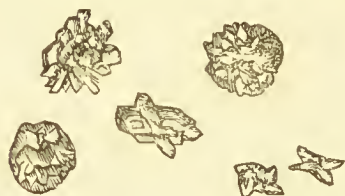
reduces Fehling's solution, and it gives a yellow crystalline precipitate when heated with a dilute solution of phosphomolybdic acid, being previously acidified with nitric acid.

It renders red litmus blue, and nitrate of silver and bichloride of mercury precipitate it.

Quantitative Analysis.—The crystals of chloride of zinc and creatinine which precipitate as above are collected on a tared filter, washed with alcohol, and dried at 100° C. Let p represent the quantity of chloride of zinc and creatinine obtained from 300 c.c. of urine, then $p \times \frac{62.44}{100} = x$, or the amount of creatinine contained in the same volume. In order to obtain the weight of creatinine per litre, divide the result x by 3, and then multiply by 10.

Physiology and Pathology.—A healthy individual on a mixed dietary eliminates, on an average, 1 gramme of creatinine in twenty-four hours, or, according to Neubauer, 0.60 to 1.20. A highly nitrogenous diet augments the proportion. It is also augmented in acute febrile diseases, as in pneumonia, typhoid fever, intermittent fever, tetanus, etc. It diminishes, on the

contrary, during convalescence from these diseases, and likewise in anæmia, chlorosis, muscular atrophy, tuberculosis, paralysis, etc.



XANTHINE AND HYPOXANTHINE.



FIG. 25.—HYDROCHLORATE AND NITRATE OF XANTHINE.

Xanthine ($C_5H_4N_4O_2$) exists but in very small quantity in normal urine (1 gramme in 300 litres). It is found throughout the entire organism. Scherer has found it in the spleen, the pancreas, and the brain. It is found in certain forms of

urinary calculi of rare form. It is increased in the urine in leucocythæmia.

It appears in the form of a white waxy body, sparingly soluble in water, and insoluble in alcohol and in ether. It is soluble in ammonia, potash, and caustic soda. With hydrochloric and nitric acid it forms crystalline salts. It is precipitated from its ammoniacal solution by chloride of zinc, chloride of calcium, and acetate of lead, and from a hot aqueous solution by acetate of copper and binoxide of mercury. If xanthine be evaporated with nitric acid, a yellow residue is obtained, which on addition of potash becomes of a yellowish red when cold, and of a violet red on being heated. When a particle of xanthine is deposited on a mixture of caustic soda and a little chloride of lime, it encircles itself with a deep green zone, which soon passes into brown and disappears.

Hypoxanthine ($C_5H_4N_4O$), or *Sarcine*, is not regarded as a normal constituent of urine. It is a body closely resembling xanthine, and is found in different organs of the body, such as the liver, the spleen, and pancreas, and sometimes in the urine in cases of leucocythæmia. Hypoxanthine is changed into xanthine by oxidation. When evaporated with nitric acid, hypoxanthine gives a yellow stain, which, on addition of caustic soda, does not become reddish-yellow.

OXALURIC ACID.

Oxaluric Acid ($C_3H_4N_2O_4$).—This acid constitutes one of the derivatives of uric acid, and its presence has been demonstrated in normal urine. According to Schunck and Neubauer, it exists in small portions in the urine in the condition of an ammoniacal salt, and exhibits the form of a fine crystalline powder of acid taste, and very insoluble in water. Oxalurate of ammonia is, on the contrary, very soluble in water. It crystallizes in the form of long prismatic crystals united together in tufts or rosettes.

ALLANTOINE.

Allantoine ($C_4H_6N_4O_3$) is a characteristic constituent of the *liquor amnii*. It is found in the urine after the internal administration of uric acid, in foetal urine, and in the urine of

newborn children, in which it may continue for some days. It crystallizes in transparent, rhomboidal, colourless prisms, which

are soluble in 160 parts of cold water, more soluble in boiling water and alcohol, and insoluble in cold alcohol or ether.

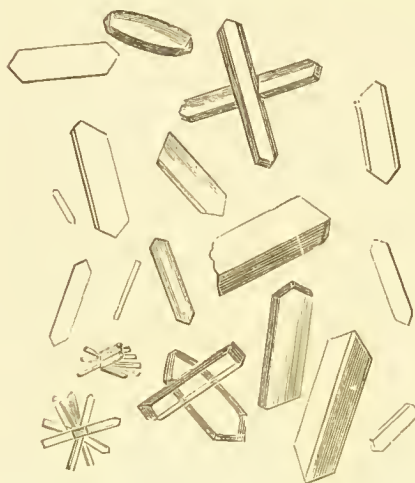


FIG. 26.—ALLANTOINE.

unchanged in the air. One hundred parts of water dissolve 5.14 grammes at a temperature of 15° C., and at a temperature of 100° C. 100 grammes of water dissolve 120 of acid. It is not very soluble in alcohol, and less so in ether. With alkalis it forms soluble combinations.

Extraction.—Precipitate the urine with baryta, eliminate the baryta with an excess of sulphuric acid, and evaporate. Then acidify strongly with a concentrated solution of sulphuric acid, and agitate with ether. Eliminate the ether by distillation, treat the residue with water, heat to ebullition, and during the process add drop by drop pure nitric acid until the

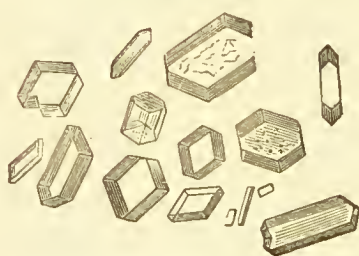


FIG. 27.—SUCCINIC ACID.

liquid presents a permanent yellow colour. After concentration of the liquid, succinic acid separates in a crystalline form. The nitric acid destroys all the impurities without attacking the succinic acid.

SUCCINIC ACID.

Succinic Acid ($C_4H_6O_4$) has been found in normal urine by Meissner and Shépard. When benzoic acid is ingested its quantity is augmented. Succinic acid crystallizes in hexagonal tables, which are odourless and colourless, and remain

Tests.—An aqueous solution of succinic acid accurately neutralized by an alkali gives, with perchloride of iron, a reddish precipitate, which is insoluble in mineral acids. A fragment of succinic acid heated in a test-tube evolves white vapours of a nature irritating to the tracheal mucous membrane. The solution, or that of its combination with potash or soda, gives a white precipitate with alcohol.

BENZOIC ACID.

Benzoic Acid ($\text{HC}_7\text{H}_5\text{O}_2$) is not a normal constituent of urine, but is found in it during putrefaction, being derived from hippuric acid. It is found in the urine after the ingestion of benzoic acid, or of substances which are transformed in the organism into this acid, such as cinnamon, benzoin balsam, balsam of tolu, quinine, prunes, etc. Benzoic acid crystallizes in the form of fine colourless needles or brilliant scales. It sublimes at 240°C . without decomposition, and is very soluble in ether. It is difficult of solution in cold water, but dissolves more readily in boiling water. Alcohol, ether, acetic acid, and petroleum-ether dissolve it readily. Its solutions redden litmus, and with alkalies it forms salts soluble in water and in alcohol.

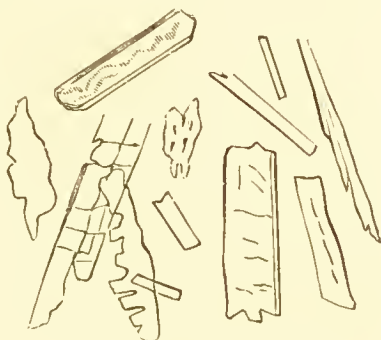


FIG. 28.—BENZOIC ACID.

Extraction.—In order to extract it from the urine, the liquid is concentrated to the consistence of an extract, and then treated with alcohol. The alcohol is removed by evaporation, and the aqueous residue is treated with hydrochloric acid, whereupon the benzoic acid separates.

OXALIC ACID.

Oxalic Acid — Oxalate of Lime ($\text{C}_2\text{H}_2\text{O}_4 + 2\text{H}_2\text{O}$).—The most important of the non-nitrogenous organic acids of the urine is oxalic acid. It is frequently found in the urine, but only in small quantity, amounting to about 2 grammes in twenty-four

hours. It is found under the form of oxalate of lime, in which combination it forms the greater part of the 'mulberry calculus.' It crystallizes in rhomboidal colourless crystals, soluble in water and in alcohol.

Oxalate of lime forms small square, brilliant, octahedral crystals, which are perfectly transparent, strongly refract light, and present the appearance of an ordinary letter envelope. At other times it presents a lozenge form, or that of a triangle with terminal pyramids, and is not unfrequently found in the 'dumb-bell' form. Oxalate of lime is insoluble in water, sparingly

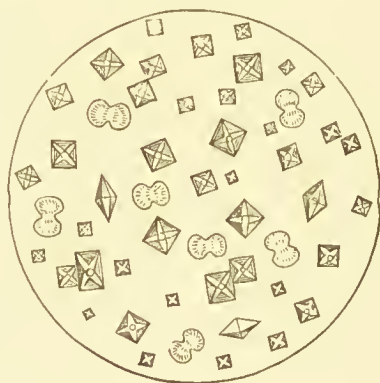


FIG. 29.—OXALATE OF LIME.

soluble in acetic acid, but is easily soluble in hydrochloric and nitric acid. It also dissolves in acid phosphate of soda, which accounts for its being found in solution in the urine.

Detection and Isolation from Urine.—Mix from 400 to 600 c.c. of urine with a solution of chloride of sodium, saturate with ammonia, and redissolve with acetic acid the precipitate which forms, avoiding an excess of the acid. At the end of twenty-four hours a new precipitate forms, in which oxalate of lime is found with uric acid. The precipitate is gathered on a filter, washed with water, and treated with a few drops of hot hydrochloric acid, which dissolves the oxalate of lime, leaving the uric acid. The filtered liquid is then collected in a test-tube, diluted with 15 c.c. of water, and very dilute ammonia added drop by drop. After an interval of some hours, oxalate of lime

is deposited, which may be recognised on microscopic examination by its characteristic appearance.

Quantitative Analysis.—The crystals are collected on a small filter, washed with warm water, and dried. Having detached them from the filter, the latter is incinerated in a tared platinum capsule; then the crystals are added and calcined at a faint red heat. When thus treated, the oxalate of lime is transformed into carbonate of lime. In order to change into carbonate the portion which may have been transformed into caustic lime, the cold residue is saturated with carbonate of ammonia, slowly evaporated to dryness, and ignited as above; this process being repeated till the weight no longer increases. There but remains to weigh the residual carbonate of lime, of which 100 parts correspond to 135 crystallized oxalate of lime.

Physiology and Pathology.—The presence of oxalate of lime in urine may be due to mere disturbances of digestion. It may be derived from the ingestion of certain aliments, such as rhubarb, sorrel, tomatoes, chicory, ginger, etc., and as the result of poisoning by salt of sorrel (binoxalate of potash). In cases of physiological oxaluria, the urine deposits crystals of oxalate of lime, even when it contains but minute proportions, the acidity of the urine being insufficient to maintain in solution all the oxalate eliminated by the kidney. Oxalic acid results from the oxidation of the hydrocarbons, the albuminoids, and the fatty and saccharine constituents of the body. Oxalate of lime frequently occurs in the urine in cases of nervous affections, and especially where there is embarrassment of the respiration from this cause. In cases of diabetes there is an augmented excretion of oxalic acid, and sometimes, when the sugar diminishes, it does so in greater proportion than oxalic acid, and *vice versa*.

As constituting an essential disease, as described by Begbie, oxalate of lime may continue for a long time in the urine, and cause the state known as the *oxalic acid diathesis*. In cases of spermatorrhœa, in common with other observers, I have frequently found oxalate of lime in the urine. Chronic prostatitis may in these cases, to some extent, account for its formation.

VOLATILE ACIDS (PHENOLS).

Under the volatile acids, or phenols, are comprised bodies containing at least six atoms of carbon. Several of these constituents exist in the urine. The phenols properly so called—viz., *phenic* or *carbolic acid*, *paracresol*, and *pyrocatechin*—are found in the urine with potash.

Phenic Acid (C_6H_5OH) is found with indol and skatol during putrefactive decomposition of proteids. Its homologue paracresol (C_6H_4OH,CH_3) is not found free in urine, but exists as cresylsulphuric acid (C_7H_7O,SO_2OH). The amount of phenic acid in urine notably augments when this agent is used either by external application or internal administration. When present in the urine, the fluid presents a greenish-brown colour, which on contact with air changes into a dark brown. This is due to the formation of hydroquinone, the consequence of the absorption of oxygen by the phenic acid.

Detection in Urine.—In order to isolate phenic acid from urine, treat 200 c.c. of the fluid with 40 c.c. of hydrochloric acid, and distil to about 150 c.c. Filter a little of the fluid, and add a little bromine water, when, if the urine contain phenic acid, a flocculent yellowish-white precipitate is obtained, which is more or less crystalline, and evolves the odour of phenic acid. Perchloride of iron causes a violet colour, and Millon's reagent hot, a red colour. A mixture of aniline and hypochlorite of sodium gives a blue colour, which passes into red, and which alkalies restore to blue.

Hydroquinone ($C_6H_4(OH)_2$) — Paradioxybenzol — is not a normal constituent of urine, but results from the ingestion of phenic acid and benzol. As found in the urine, it is an ethereal compound with sulphuric acid. The dark colour which urine containing phenic acid assumes on exposure to air is due to it. In common with pyrocatechin, it reduces metallic salts, but unlike it, it is nearly insoluble in cold benzol, and the two may be thus separated.

Pyrocatechin, or *Alkaptonic* ($C_6H_4O_2$), occurs in the urine after the ingestion of phenic acid and benzol. Urine which

contains pyrocatechin, left in contact with air, assumes a dark-brown colour, owing to the formation of hydroquinone, as obtains in the case of phenic acid. The same change occurs after the administration of naphthaline, aniline, salicylic acid, and arbutine. A dilute solution of ferric chloride turns solutions of pyrocatechine into an emerald-green colour. If this solution be then acidulated with tartaric acid, it becomes violet on addition of ammonia, and purplish-red on the addition of an excess; the green colour may again be restored by an excess of acetic acid. It is distinguished from hydroquinone by yielding a precipitate with normal acetate of lead, which is soluble in acetic acid. The occurrence of this substance in the urine of herbivora is probably due to certain constituents of their food.

Indol (C_8H_7N) occurs in the fæces with *skatol*, occasioning the characteristic odour. It arises from the putrefactive decomposition of proteids. **Skatol** (C_9H_9N) has a similar origin. It is found in the urine in the form of skatoxysulphate of potash. When urine contains skatol, the addition of hydrochloric acid and chloride of lime causes a violet tint, which is unaffected by ether and chloroform. Robin regards skatol as a normal constituent of urine, and as being allied to urobiline urobrythrine.

COLOURING MATTERS.

It is still doubtful to which pigment the colour of the urine is due. In all probability it is due to more than one, which result from the oxidation of the chromogenous principles.

Urobiline ($C_{32}H_{40}N_4O_7$).—This principle was discovered by Jaffé and obtained by Maly, who named it ‘hydrobilirubine,’ by the action of an amalgam of sodium on bilirubine. Urobiline exists, but rarely fully formed, in normal urine at the period of emission. It is, however, produced when a mineral acid is added to urine and the fluid exposed to air. The urine is thus supposed to contain a chromogenous principle, which gives origin to it. It is usually believed to be derived from bilirubine and biliverdine by a process of reduction in the intestines. According to Hayem,* the bile may contain urobiline, and it

* *Le Progrès Medical*, August 6, 1887.

may be produced as a pigment by this organ when it is torpid or in a diseased condition.

Properties of Urobiline.—Normal urobiline is an oxidation product of effete hæmatin and bile pigments. It is an amorphous substance of a brownish-red colour, very sparingly soluble in water, but easily soluble in alcohol and chloroform, and less easily in ether. Its solutions when concentrated are of a dark-brown colour, passing to reddish-yellow, and to rose colour by dilution. Neutral solutions of urobiline present a beautiful fluorescent green, which is destroyed by an acid, but restored by neutralization by an alkali. On spectroscopic examination a black band is found to exist between the green and the blue.

Reaction.—Urine containing urobiline presents a rose or yellowish-rose colour, according to the amount of the colouring matter present; on the addition of ammonia the tint becomes clearer, passing to green. Nitric acid causes a reddish-brown colour, which passes to a violet-red or blue on addition of hydrochloric or sulphuric acid. If 100 c.c. of urine be agitated with half its volume of ether, and if the latter be evaporated, a residue is obtained, which, on the addition of a little absolute alcohol gives a rose coloration and an intense green fluorescence.

Pathology.—Urobiline exists in augmented amount in the urine in all febrile affections, such as acute gout, pneumonia, pleurisy, rheumatism, gastric derangements, and as the result of various internal hæmorrhages. It is especially augmented in certain diseases of the liver, such as cirrhosis, and all pathological states which occasion an exaggerated destruction of the red globules of the blood. Urobilinuria appears to be linked with an alteration of the liver cells; in this case the bile is decolorized, and contains a marked quantity of urobiline. This alone will not cause jaundice. In the *hamapheic jaundice* of Gubler, other colouring matters than urobiline exist in the urine, arising from intra-organic modifications of bilirubine and biliverdine. MacMunn has described two bodies allied to urobiline — viz., *febrile urobiline* and *urohæmatoporphyrine*. The latter pigment can be separated from urine in the same manner as urobiline. It has been found in Addison's disease,

acute rheumatism, cirrhosis of the liver, croupous pneumonia, pericarditis, Hodgkin's disease, etc.

Urochrome and Uroerythrine (*ὀύρον*, urine, and *ἐρυθρός*, red). —Thudichum considers that the urine contains but one pigment, which he has named *urochrome*. It is a product much less defined than urobiline, with which Maly, indeed, considers it identical.* It is a yellow substance, which dissolves with difficulty in alcohol, but easily in ether. On becoming oxidized in contact with air, urochrome becomes converted into a red body, to which Heller has given the name *uroerythrine*. This constitutes the colouring matter of the pink urates. It is found also with urobiline in the red deposits of uric acid. The deep reddish-yellow colour of the urine of acute rheumatism, affections of the liver, etc., is due to products of uroerythrine. It is stated that the red principle of uroerythrine submitted to the influence of oxidizing agents is transformed into three substances: A dark powder, *uromelanine* (*μελας*, black— $C_{36}H_{43}N_7O_{10}$), which is soluble in potash, and appears to perform the rôle of an acid. The alcoholic solution, which is coloured ruby-red, gives on the addition of water a precipitate of a resinous aspect, which is separable by ether into two parts, the one insoluble in that liquid, *uropittine* (*πίττα*, pitch— $C_9H_{10}N_2O_3$), which is soluble in alcohol, and the other, *omicholic acid*, insoluble in ether.

Indican ($C_8H_6NSO_4K$). — Indican, or the *uroxanthine* of Heller, is always found in normal urine, but only to the extent of from 5 to 20 milligrammes in twenty-four hours. Its proportion is notably augmented in cases of intestinal obstruction, diffuse peritonitis, cholera, cancer of the liver and stomach, and pernicious anæmia.

Under the influence of oxidizing agents, indican is transformed into two other pigments—the one blue, *uroglauine* or *indigo-tine*, the other red, *urrhodine* or *indirubine*. The same doubling takes place when urine containing indican enters into putrefaction; and if the chromogen is in notable quantity, agitation in air causes the urine to become of a violet-blue colour. In rare cases the transformation of indican takes place in the urinary passages, when the urine is emitted of a blue

* Liebig's Ann., Bd. clxviii. (1872), S. 90.

colour. Uroglaucone and urrhodine have also been found in sediments and urinary calculi.

Tests.—Boil urine with a tenth of its volume of hydrochloric acid, or treat it cold with two or three times its volume of the same acid, when, if it contains indican, a violet coloration ensues. As a control test, agitate the same urine with ether, which will take up the urrhodine produced at the same time. Urine containing albumen is also coloured violet by hydrochloric acid; but the albumen may be removed by coagulation, and recognised by its own special tests. M. Obermayer* recommends that the urine be treated with a solution of acetate of lead, avoiding an excess, and filtered; the filtrate is now agitated with an equal volume of hydrochloric acid, containing from 2 to 4 per cent. of perchloride of iron; a little chloroform is then added, which gives a transparent liquid of a pure blue colour.

Uroglaucone (Indigo blue.— $C_{16}H_{10}N_2O_2 + 2H_2O$).—This principle, by its composition and properties, resembles vegetable indigo, in appearing as an amorphous powder composed of microscopic crystals. It is insoluble in water, sparingly soluble in concentrated alcohol and boiling ether; it is more soluble in cold chloroform. In order to separate uroglaucone from the urine, the fluid is filtered, the blue matter remaining on the filter is treated with concentrated boiling alcohol; a violet solution is thus obtained. This is evaporated, the residue washed with cold water, and redissolved in boiling alcohol. On carefully evaporating, blue prismatic crystals of uroglaucone are deposited. In order to extract uroglaucone from sediments, the sediment is washed on a filter, at first with hydrochloric acid, then with water, and the dried filter is exhausted with chloroform.

Urrhodine, or indirubine (indigo red), is a brown amorphous substance, insoluble in water, but soluble in alcohol, ether, and chloroform. Its solutions are of a red colour. In order to separate urrhodine from the urine, it is acidified with a little hydrochloric or acetic acid, filtered, and agitated with chloroform or ether. The solvent is then evaporated, and the urrhodine

* *Chemis. Centralblatt*, 1890, p. 273, and *Pharm. Zeits. für Russ.*, xxix., 1890, 504.

remains. This pigment is easily removed with cold alcohol or ether.

PATHOLOGICAL SIGNIFICANCE OF URINE,

As from Colour and Density.

Pale urine emitted in average quantity and of feeble density indicates, in the first place, that there is no acute febrile affection. Pale urine, abundantly secreted, of a low specific gravity, points to cirrhosis of the kidney, with desquamation of renal epithelium, and unfavourable prognosis. Here uræmia threatens. In anæmia the urine is pale and of low specific gravity; chloro-anæmia is revealed, not only by the pallor of the mucous membranes, but by the decoloration of the urine. In this case there is a deficiency of red globules, and consequently of hæmoglobin, whereby oxidation is diminished, and hence the normal colouring matters of the urine thus formed are in lessened quantity. Thudichum therefore properly regards the absence of urochrome in the urine, and its retention in the organism, or rather, perhaps, its non-formation, as one of the characteristics of anæmia. Urochrome retained in the system oxidizes gradually, giving origin to omicholic acid and uropittine, which are found in the tissues, and in the tartar of the teeth, and are thus a cause of fætidity of breath.

In hysteria large quantities of pale urine are secreted, as after the ingestion of large draughts of water, or the use of diuretics and alcohol.

When the urine is strongly coloured yellow, it is usually found to contain indican, as in cases of cholera. It is of a like colour after the ingestion of substances containing crysophanic acid, as santonine, rhubarb, senna, etc. These urines become red on the addition of an alkali.

Red Urines are usually of a high density, and are rich in solid principles. Such is the urine secreted during night, and the urine of febrile affections generally. Sediments of urate of soda are usually whitish, but other urates are of a brick colour, or almost red, from containing a large amount of colouring matter. When the urine undergoes putrefaction, indican is

transformed into uroglaucine and indirubine (urrhodine). Uroglaucine and urrhodine rarely form in the bladder. They are sometimes found in cases of Bright's disease and in catarrh of the bladder, when the urine has become ammoniacal. The two substances may be separated by ether.

Brown Urines usually contain abnormal colouring matters, such as those of the bile and blood. In cases of melanotic cancer the urine is black, from the presence of *melanin*. Where iodine and bromine have been taken to a considerable extent, the addition of nitric acid to the urine causes the appearance of a brown colour from the liberation of the iodine and bromine.

TO ESTIMATE THE TOTAL NITROGEN OF THE URINE.

The following is **Kjaldahl's Method**, modified by Pflüger and Bohland: Take 5 c.c. of urine of average concentration, and place in an Erlenmeyer's flask holding 300 c.c., together with 20 c.c. of concentrated sulphuric acid; boil the mixture on wire-gauze, over a large Bunsen flame, until all water and gases formed are driven off. The fluid at first becomes black, but afterwards of a yellow tint, when the heat should be diminished. From twenty-five or thirty minutes are required for the heating. The fluid is then allowed to cool, diluted with water to 200 c.c., and placed in a flask; 80 c.c. of caustic soda solution, of a specific gravity of 1.3, are then added, the flask speedily corked, and its contents distilled into a measured quantity of standardized sulphuric acid.

The nitrogen of the urine is converted by this process into ammonia. The ammonia combines with the sulphuric acid, and the quantity of ammonia formed is at once known if we know the amount of sulphuric acid which has been neutralized. The excess of sulphuric acid is determined by titration with standard caustic soda, and this excess deducted from the quantity of sulphuric acid originally taken gives the amount which has been neutralized. The ammonia thus determined is easily calculated to nitrogen, 17 parts of ammonia containing 14 parts of the latter.

CHAPTER III.

NORMAL ELEMENTS OF THE URINE.

Inorganic Substances.

CHLORIDE OF SODIUM.

Chloride of Sodium—Qualitative and Quantitative Analysis—Pathological Significance—Sulphuric Acid and Sulphates—Analysis—Quantitative Analysis of Sulphuric Acid and of Sulphur—Pathological Significance—Phosphoric Acid and Phosphates—Phosphoglyceric Acid—Qualitative and Quantitative Analysis of Phosphoric Acid—Variations of Phosphoric Acid in Urine—Potash Soda—Lime—Magnesia—Qualitative Analysis—Ammonia—Iron—Nitric Acid and Nitrates and Nitrites—Silica—Peroxide of Hydrogen—Gases in Urine.

NEXT to urea, ehloride of sodium is the most abundant element of the urine, of which it forms almost two-thirds of the mineral substances. The *ehlorides of potassium*, of *calcium*, and of *magnesium* exist only in feeble proportions in urine.

In the normal condition the amount of ehloride of sodium eliminated by the urine in twenty-four hours is from 10 to 13 grammes. Corresponding to the quantity of food ingested, it necessarily varies.

Chloride of sodium is a colourless, inodorous salt, of great solubility in water, and little soluble in alcohol. When a solution of ehloride of sodium is evaporated on a glass slide, it separates from solution in the form of cubic crystals; from evaporated urine it deposits as octahedral and tetrahedral crystals. Solutions of ehloride of sodium, in common with ehlorides of potassium, calcium, and magnesium, give a white precipitate

with nitrate of silver, insoluble in nitric acid, but easily soluble in ammonia, and which blackens on exposure to light.

Qualitative Analysis. — On microscopic examination, the characteristic octahedral crystals are recognised. These crystals communicate to the flame of alcohol a yellow colour. Add to urine so as to render it strongly acid a few drops of nitric acid, and then a few drops of a solution of nitrate of silver. A white, dense precipitate of chloride of silver is formed. Nitric acid is added in this case to prevent the precipitation of other salts of silver, especially the phosphate.

Quantitative Analysis.—This is accomplished by means of a titrated solution of nitrate of silver, which contains 29·062 grammes per litre.

The process of Mohr is based upon the fact that by the addition of nitrate of silver to urine containing neutral chromate of potash all the silver is precipitated, in the first place, in the form of chloride of silver, and ultimately of chromate of silver, the latter appearing as a red precipitate. By means of a graduated pipette pour into a glass jar 10 c.c. of urine, to which add 0·5 c.c. of a concentrated solution of neutral chromate of potash. Introduce the standard solution of nitrate of silver, of which each c.c. precipitates 0·010 gramme of chloride of sodium by means of a graduated burette. Add drop by drop, constantly agitating until the red coloration which is produced at the lines of contact of the two fluids does not disappear. The first trace of the red colour indicates the end of the reaction. Note the quantity of the nitrate of silver solution employed, when the amount of chloride is easily calculated. Owing to various circumstances, this method is not absolutely accurate, and in order to ensure greater accuracy, all the organic matter should be decomposed by nitric acid.

To the clinician, an approximation of the quantity of chloride of sodium is usually sufficient. To ascertain this, add to urine previously acidified by nitric acid a strong solution of nitrate of silver (8 per cent. or thereby). If the quantity of the chloride is normal, a compact whitish-gray, caseous precipitate is formed, which deposits readily, and separates on agitation in whitish flakes. Ultimately these flakes deposit, and leave a clear super-

natant fluid. The smaller the quantity of the chloride of sodium, the less dense is the precipitate. When the quantity is very small, a milky colour alone is produced.

The following modification of the silver process has been suggested by Freund and Töpfer (*Centralb. f. Klin. Medic.*, 1892, N. 38, p. 801). To urine is to be added a solution containing 3 per cent. of acetic acid and 10 per cent. of acid acetate of soda, by which the precipitation of uric acid, xanthine, and colouring matters is prevented in the form of precipitate with acid nitrate of silver. To 5 or 10 c.c. of urine add 15 or 20 c.c. of water. To the urine thus diluted add 25 c.c. of the acetic solution, a few drops of a 10 per cent. solution of bichromate of potash, and finally the nitrate of silver solution, prepared after Mohr's method.

Pathological Significance. — (1) *In all febrile affections* (especially in pneumonia) there is a diminution of the chloride of sodium in the urine. According to Vogel, in intermittent fever the elimination of chloride of sodium is more considerable in the febrile stage than during the apyretic intervals. The complete disappearance of chloride of sodium in febrile affections is of grave import, its reappearance being of favourable significance.

(2) *In chronic affections* the quantity of chloride of sodium and of urea is proportionate to the general nutrition.

(3) *In renal affections*, with albuminuria or anasarca, there is augmentation of the chlorides when previous retention of these salts occurred. When absorption of the exudations which contain a large proportion of chloride of sodium takes place, the chloride of sodium in the urine may amount to almost 55 grammes in twenty-four hours.

SULPHURIC ACID AND SULPHATES.

Sulphuric acid is found in the urine in two forms — viz., in combination with sodium and potassium as sulphates, and in combination with phenols. In the normal condition the quantity of sulphuric acid united with the latter forms but the tenth part of the total sulphuric acid. Almost all the normal sulphuric acid of the urine is combined with potash and soda in nearly equal proportions, and hence in analysis the

proportion of acid alone is indicated, the base with which it is combined not being considered.

Analysis.—The presence of sulphuric acid is demonstrated in the following manner: Strongly acidify the urine with acetic acid, and add a solution of chloride of barium. A fine granular, white precipitate of sulphate of barium, insoluble in hydrochloric, nitric, and acetic acids, results. When the sulphuric acid is combined with the phenols, mix urine strongly acidified by acetic acid with an excess of chloride of barium, and filter. Add hydrochloric acid to the filtrate, when a second precipitate of sulphate of barium is formed. Sulphur exists in the urine in infinitesimal quantity independently of that contained in the sulphuric acid. To detect this, add to urine hydrochloric acid, so as to render it strongly acid, and remove all the sulphuric acid by digestion with chloride of barium, and treat the liquid with pure carbonate of soda, filter, add a little saltpetre to the filtrate, and evaporate. Ignite the residue, add pure hydrochloric acid, and evaporate several times to dryness with hydrochloric acid until all the nitric acid is expelled. Finally, dissolve the residue in water. The solution will contain the sulphur in the form of sulphuric acid, and give a precipitate with hydrochloric acid and chloride of barium.

Quantitative Analysis of Sulphuric Acid.—Into a conical glass vessel pour, with two or three volumes of water, 25 to 50 c.c. of filtered urine. Acidify strongly with hydrochloric acid, heat almost to boiling, and precipitate with an excess of chloride of barium, and expose to moderate heat. When the liquid has become clear, separate the supernatant fluid from the precipitate. Wash the latter with boiling water, decant anew on the filter, and continue the operation until the water of the washing is no longer acid. Finally, place the precipitate on a filter, and wash with boiling alcohol. Dry the filter and its contents at a heat under 100° , ignite in a tared platinum capsule, cool, and pour on the residue a few drops of nitric acid, heat to a dull red, add one or two drops of sulphuric acid, and heat anew. Finally, heat the precipitate to bright redness. If the cold residue is not entirely white, calcine anew after the addition of nitric and sulphuric acid, and weigh after cooling. From the

ascertained weight deduct that of the capsule. The difference represents the weight of the sulphate of barium, and this, multiplied by 0·34335 or by 0·4206, gives the proportion of anhydrous sulphuric acid (SO_3) or of H_2SO_4 contained in the volume of urine analyzed.

Quantitative Analysis of the Total Sulphur.—Mix 50 c.c. of urine with a few grammes of carbonate of soda and nitrate of potash. Evaporate to dryness in a platinum capsule. Dissolve in water, and expel the nitric acid by successive evaporations with hydrochloric acid. Finally, dissolve the residue in water, and ascertain the amount of sulphuric acid. The determined weight of anhydrous acid multiplied by 0·400 gives the proportion of total sulphur, and if from this weight be subtracted the acid of the sulphates and the sulpho-organic acids, the difference, multiplied by 0·400, represents the sulphur other than that in the state of sulphuric acid.

Sulphuric acid is augmented in the urine by large ingestion of animal food, of sulphuric acid itself, of sulphur combinations, the use of *cruciferae* (cauliflower, turnip, etc.). It is diminished by all other forms of vegetables.

Pathological Significance.—In acute febrile diseases sulphuric acid is but feebly augmented in the urine. In the early stages of typhoid fever it is little above the normal in amount, while during convalescence it is less. In pneumonia and acute myelitis the augmentation is considerable. In such chronic affections as leukæmia, polyuric and glycosuric diabetes, and progressive muscular atrophy, it is augmented; in certain diseases of the kidney it is diminished in the urine.

PHOSPHORIC ACID AND PHOSPHATES.

Normally the urine contains phosphoric acid in combination with different bases. It frequently enters into the composition of various calculi and urinary sediments.

Properties of Phosphates.—Phosphoric acid is tribasic, and forms three varieties of salts: basic salts, neutral salts, and acid salts.

Alkaline phosphates are soluble in water, and insoluble in alcohol; *earthy phosphates* are insoluble in water, sparingly

soluble in water charged with carbonic acid gas, insoluble in alkalies, and very soluble in mineral acids, in acetic acid, and in solutions of acid salts.

With chlorides of barium or calcium and ammonia, phosphates give a flocculent precipitate insoluble in ammonia, but soluble in mineral acids. When a magnesium salt is added to a solution of the phosphates, a white crystalline precipitate of triple phosphate is formed, which is soluble in acids, but insoluble in ammonia. Ferric chloride added to a solution of phosphates, containing no other free acid but acetic acid, causes a yellow flocculent precipitate of ferric phosphate.

Molybdate of ammonia in nitric acid gives a yellow precipitate with phosphates, slowly in the cold, but more rapidly with heat. Phosphate solutions, on addition of acetate of soda, give with acetate of uranium a yellow precipitate of phosphate of uranium, soluble in mineral acids, but insoluble in acetic acid.

Phosphates of the Urine.—Phosphoric acid is found in the urine united with soda, potash, lime, and magnesia as bases.



FIG. 30.—STELLAR PHOSPHATES OF LIME.

Two-thirds of the total weight of *earthy phosphates* (magnesium and calcium) are represented by phosphate of magnesium, the other third by phosphate of calcium.

While the earthy phosphates are insoluble in water, they are,

Generally the alkaline phosphates (sodium and potassium) represent three-fourths of the amount of phosphates eliminated in twenty-four hours. Of the two alkaline phosphates, phosphate of sodium exists in larger quantity than that of potassium. These two salts exist in the state of acid phosphates, and it is to them chiefly that the acidity of normal urine is due.

nevertheless, kept in solution in the urine by means of the carbonic acid and the acid salts, especially the acid phosphate of sodium contained in the urine. When the acidity of the urine is neutralized by the addition of an excess of ammonia, or when it has undergone the ammoniacal fermentation and has become alkaline, the phosphate of lime, which is insoluble in alkaline liquors, is most frequently precipitated in an amorphous form, the phosphate of magnesium combining

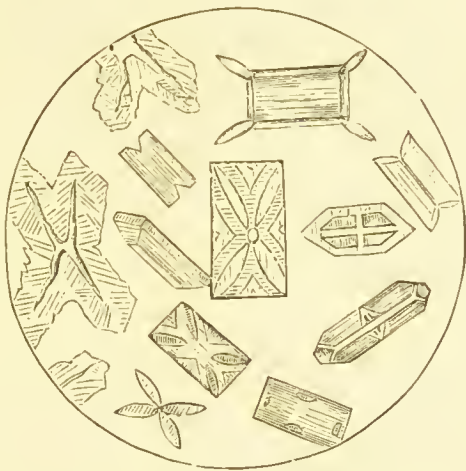


FIG. 31.—TRIPLE PHOSPHATES (PHOSPHATES OF AMMONIA AND MAGNESIA).

with the ammonia, and being precipitated under the form of ammonio-phosphate of magnesium. It is thus that the earthy phosphates are frequently observed in the urine under pathological conditions. As the urine always contains at the same time phosphate of calcium and phosphate of magnesium, the sediment is usually composed of a combination of these two phosphates.



FIG. 32.—TRIPLE PHOSPHATES (FEATHERY FORM).

Sediments are likewise produced when the urine has been rendered alkaline, or merely neutralized by a fixed alkali, such as

potash or soda, for example, in consequence of the prolonged

use of alkalis as therapeutic agents. In this case the sediment usually consists of phosphate of lime.

Phosphoglyceric Acid.—Phosphoric acid may be found in the urine in combination with glycerine, under the form of *phosphoglyceric acid*. This acid is usually found in cases of leucocythæmia. According to Lepine and Egmonnet, it is found in normal urine to the extent of 15 milligrammes per litre, and its quantity is augmented after the use of chloroform as an anæsthetic.

Qualitative Analysis of Phosphoric Acid.—The presence of phosphoric acid in the urine in combination with lime and magnesia is indicated by the precipitation of earthy phosphates by means of ammonia. In order to separate the phosphoric acid from the alkaline phosphates, filter the urine precipitated by the ammonia, and test the filtered liquid with magnesia mixture, or with a solution of uranium plus acetic acid, or with perchloride of iron, when a yellow precipitate of uranic phosphate and a white precipitate will be respectively produced.

Quantitative Analysis of Phosphoric Acid.—Of the numerous processes recommended for this purpose, the most rapid is the volumetric method proposed by Neubauer. It is based on the following reactions: Acetate or nitrate of uranium gives with acetic solutions of phosphates a yellow flocculent precipitate of constant composition; and when all the phosphoric acid is precipitated, the uranium salt added in excess gives with ferrocyanide of potassium a characteristic brown coloration. This process requires the following solutions:

(1) *A Standard Solution of Phosphoric Acid.*—Dissolve in distilled water 3·087 grammes of dry acid phosphate of ammonia, and make up the solution to 1 litre. Fifty c.c. of this solution contain 0·1 gramme of phosphoric acid.

(2) *An Acetic Solution of Acetate of Soda.*—In a little water dissolve 100 grammes of pure crystallized acetate of soda, add 50 c.c. of crystallized acetic acid, and a sufficiency of water to make up to 1 litre.

(3) *Solution of Ferrocyanide of Potassium.*—A 10 per cent. solution.

(4) *A Standard Solution of Nitrate of Uranium.*—Dissolve 20

grammes of pure and dry oxide of uranium in as little nitric acid as possible. Dilute to a litre and determine the titre as follows: Into a small beaker measure 50 c.c. of the phosphoric acid solution, then add 5 c.c. of the acetate of soda solution, and into the mixture, heated on a water-bath almost to ebullition, drop by means of a burette the solution of uranium until a precipitate ceases to form. By means of a glass rod put one drop of the liquid on a fragment of porcelain, and with a pipette add a drop of the solution of ferrocyanide of potassium. If no coloration is produced, add to the liquid $\frac{1}{2}$ c.c. of the solution of uranium, and recommence the testing with the ferrocyanide and continue until a reddish-brown coloration is produced. This being obtained, measure again 50 c.c. of the phosphoric acid solution, and add 5 c.c. of acetate of soda solution, then add at once a volume of solution of uranium equal to that primarily employed, less $\frac{1}{2}$ c.c. Heat to ebullition, add $\frac{1}{10}$ c.c. of solution of uranium and test with ferrocyanide of potassium, continuing thus until the reddish-brown colour begins to manifest itself. Then read off from the burette the volume of the uranium solution employed to obtain the coloration. Supposing the volume to be 19.8, it is easy to determine to how much phosphoric acid 1 c.c. of the uranium solution corresponds. Since 50 c.c. of the phosphoric acid solution employed for the titration contain 0.1 gramme of this acid,

19.8 of uranium solution = 0.1 gramme of phosphoric acid,

1 c.c. ,, ,, = x ,

hence $x = \frac{.1}{19.8} = 0.00505$.

Each c.c. of the uranium solution corresponds, therefore, to 0.00505 gramme phosphoric acid. To estimate the amount of phosphoric acid in the urine, proceed in the same manner as for the standardization of the uranium solution. Measure 50 c.c. of the filtered urine, and add 5 c.c. of acetate of soda solution. Heat to ebullition, and add the uranium solution until a coloration is obtained with ferrocyanide of potassium. The number of c.c. employed multiplied by 0.00505 indicates the quantity of phosphoric acid contained in 50 c.c. of urine, and this quantity multiplied by 20 gives the proportion per litre.

Freund* proposes the following method for estimating the separate amount of monobasic and dibasic phosphates when the two exist together in the urine. The method is based on the property which monobasic phosphates possess of forming with chloride of barium an insoluble precipitate—acid phosphate of barium. With a liquid containing the two phosphates the amount of whose total phosphates is known, it suffices to add chloride of barium to obtain the monobasic phosphate precipitate. The phosphorus of the precipitate being estimated, subtract from the total to obtain the amount of the dibasic combination.

Variations of Phosphoric Acid in Urine.—Phosphoric acid exists in the urine in combination with lime, magnesia and soda. It is the acid phosphate of soda which determines the acidity of the urine. An adult in good health using a mixed dietary eliminates on an average from 2 to 3 grammes of phosphoric acid in twenty-four hours. This quantity is augmented when animal food preponderates in the dietary, and also after the ingestion of phosphates or substances rich in phosphates. On the other hand, the phosphoric acid is diminished by fasting and by a vegetable dietary. The excretion of phosphoric acid is generally augmented simultaneously with that of urea and chlorides as the result of an abundant ingestion of fluids. Excessive intellectual or muscular exertion acts in a similar manner.

Pathological Significance.—In acute febrile diseases, during the first few days there is generally a diminution of phosphoric acid in the urine, and towards the termination of their course, and when death is imminent, the diminution is still more pronounced. As the fever diminishes the excretion of phosphoric acid augments, and this continues during the whole of convalescence, especially when abundant nourishment is taken. In these cases, the amount may sometimes exceed the normal. In chronic diseases the elimination of phosphoric acid depends on the functional activity of the digestive organs. Generally speaking, the earthy phosphates diminish in cerebral affections, rheuma-

* 'Ueber eine Methode zur Bestimmung von einfach-Saurem Phosphate neben Zweifach-Saurem Phosphate in Harn' (*Centralb. f. Med. Wissensch.*, 1892, No. 38, p. 689).

tism, *mollities ossium*, rickets, catarrh of the bladder, etc., while they are augmented in diseases of the spinal cord and kidneys, dropsy, atrophy of the liver, and glycosuria. In the last affection the phosphaturia is frequently accompanied by azoturia.

Tessier has described a condition to which he has given the name of 'diabetic phosphaturia,' or 'phosphaturia,' which is accompanied by disorders of the nervous system and pulmonary complications. He considers this state as symptomatic of tuberculosis, or to indicate latent glycosuria. Bouchard has arrived at the following conclusions on this subject:

(1) In the majority of cases of diabetic glycosuria, and especially in cases of moderate gravity, with a small elimination of sugar and urea, phosphates are eliminated in a normal amount, or even to a less extent than normal.

(2) The augmentation of the glycosuria may be accompanied by a parallel augmentation of phosphates.

(3) When disassimilation is augmented in the diabetic, and the sugar is above the normal in quantity, this disassimilation takes place at the expense of the tissues which furnish the urea and the phosphoric acid, so that azoturia accompanies the phosphaturia, and *vice versâ*.

(4) The parallelism between the elimination of the urea and that of the phosphates takes place only in the cases in which the elimination is above the normal. Anazoturia may be observed with a normal elimination of phosphates, and hypophosphaturia with a normal excretion of urea.

(5) It appears that phosphaturia is far from being the rule in saccharine diabetes.

When phosphates deposit in the urine, a short time after emission it assumes a milky appearance. At the moment of emission it is clear. Heat precipitates the phosphates, which are dissolved by a drop or two of acetic acid.

Microscopic examination shows the characteristic forms of phosphates.

POTASH, SODA, LIME, MAGNESIA.

These bases exist in the urine in the form of chlorides, sulphates, and phosphates.

Potash and Soda.—A healthy man, on a mixed diet, eliminates in twenty-four hours 2 to 3 grammes of potash, and 4 to 6 grammes of soda. In febrile affections the excretion of potash is three or four times greater; while that of the soda diminishes when the fever is at its height, but rapidly augments during its decline. After the ingestion of potash and soda salts, the urine presents a notable augmentation in fixed alkalies.

Qualitative Analysis.—To 100 c.c. of urine add a little hydrochloric acid, and then two volumes of a clear mixture of equal parts of alcohol and ether, with a little chloride of platinum. After a few hours there are deposited crystals of chloride of platinum and potassium, mixed with chloride of platinum and ammonia, whose octahedral form is characteristic. In the case of soda, evaporate the urine in a water-bath until crystallization takes place. A portion of the crystalline mass, introduced into gas-flame, imparts to it an intense yellow colour, whose spectrum exhibits a yellow ray coinciding with the line D of the solar spectrum.

Quantitative Analysis.—The weight of the double chloride of platinum and potassium multiplied by 0.3051 gives the weight of the chloride of potassium; the difference represents the weight of the chloride of sodium. To obtain the quantity of potash and soda multiply the weight of the chloride of potassium by 0.6317, and by 0.5302, the weight of the chloride of sodium.

Lime and Magnesia.—According to Neubauer, a healthy man excretes between 0.12 and 0.25 gramme of lime in twenty-four hours, and from 0.18 to 0.28 gramme of magnesia in the same time. Lime and magnesia exist in normal urine under the form of phosphates, and in pathological urine as sulphates, oxalates, and urates.

The presence of lime and magnesia is thus demonstrated: Precipitate the urine by ammonia; dissolve the precipitate, which is a mixture of basic phosphate of lime and of ammonio-phosphate of magnesia, in acetic acid; then add a small portion of chloride of ammonium, and finally a solution of oxalate of ammonia, by which the lime is precipitated in the form of oxalate, while the magnesia remains in solution. To demon-

strate the latter, add ammonia to the filtered liquid, when a precipitate of the triple phosphate results.

Quantitative Analysis.—The weight of the triple phosphate precipitate multiplied by 0.3604 gramme gives the weight of magnesia. To ascertain the weight of lime, precipitate 100 c.c. of urine with ammonia. Redissolve the precipitate in acetic acid, and add a sufficiency of ammonic oxalate to precipitate all the lime as oxalate. Allow the precipitate to settle, separate by filtration, ignite with the filter in a platinum crucible, when calcic oxide and carbonate result. Transfer to a flask by aid of a washing bottle, and add an excess of $\frac{N}{10}$ nitric acid. Determine the amount of acid above what is required to saturate the lime by $\frac{N}{10}$ caustic alkali, each c.c. of which is equal to 0.0028 gramme CaO.

AMMONIA.

According to Neubauer, normal urine at the moment of emission contains a small quantity of ammonia, in the form of carbonate, chloride, etc., amounting to 0.6 to 0.8 in twenty-four hours. This ammonia results from the food, the liquids ingested, and the inspired air.

Qualitative and Quantitative Analysis. (See **Abnormal Constituents of the Urine.**)

Variations in the Proportion of Ammonia in the Urine.—Ammonia is augmented in the urine by a dietary rich in animal food, and the ingestion of ammoniacal compounds, which pass into the urine without undergoing alteration, such as the salts with mineral acids, or of vegetable acids which are transformed into carbonates. In disease the amount of ammonia in the urine is above the normal. In catarrh of the bladder the urine contains ammonia in the form of carbonate, arising from the decomposition of urea in the bladder.

IRON, NITRIC ACID AND NITRATES AND NITRITES, SILICA, PEROXIDE OF HYDROGEN.

Iron.—Iron is eliminated in healthy urine, according to Magnier, to the extent of 3 to 11 milligrammes per litre in twenty-four hours.

Analysis. (See **Medicaments and Accidental Elements of the Urine.**)

Nitrates and Nitrites.—The presence of nitrates, arising from certain principles of food, has been demonstrated by Schönbein in the urine. Potable waters, peas, salads, etc., contain small quantities of nitrates. Under the influence of putrefaction in urine undisturbed, the *nitrates* are transformed into *nitrites*. In order to demonstrate the presence of nitrates, evaporate a little urine to dryness with a little potash, and treat the residue with sulphuric acid. Nitrous vapours are evolved, which impart a blue colour to iodide—starch paper. If the urine be not fresh, and if the nitrates have been transformed into nitrites, the presence of the latter is demonstrated by adding to the urine a little solution of starch and iodide of potassium, and then a few drops of water acidulated with sulphuric acid, when a blue coloration results.

SILICA.

To extract silica from urine, dissolve in a platinum crucible with an excess of carbonate of potassium and sodium the incinerated residue of from two to three litres of urine. Acidulate with hydrochloric acid, and evaporate to dryness on a water bath. Treat the residue again with hydrochloric acid and water, when the silica is found to remain in the form of a white, tasteless, and odourless powder, soluble in a boiling solution of carbonate of soda. The quantity of silica voided with the urine in twenty-four hours varies from 0.02 to 0.03 gramme.

Peroxide of Hydrogen has been shown by Schönbein to exist in normal urine. Its presence is demonstrated thus: Add to 200 c.c. of fresh urine a few drops of a solution of sulphate of indigo, so as to obtain a green coloration, and finally a small portion of a solution of the sulphate of protoxide of iron. If the

urine contains peroxide of hydrogen, the colour of the mixture changes from clear to brownish-yellow, in consequence of the discoloration of the indigo.

GASES IN THE URINE.

Carbonic Acid, Oxygen, Nitrogen.—The urine always contains in solution carbonic acid, oxygen and nitrogen. According to Morin, a litre of normal urine contains 15·957 c.c. of carbonic acid, 0·658 c.c. of oxygen, and 7·773 c.c. of nitrogen. All causes which accelerate respiration increase the amount of carbonic acid and nitrogen, and diminish that of oxygen. The combined portion of the carbonic acid is united to the alkalies and earthy salts in the form of bicarbonates. Its quantity is augmented in fevers *pari passu* with that of urea. Carbonic acid aids the solution in the urine of earthy phosphates.

PART III.

CHAPTER IV.

ABNORMAL CONSTITUENTS OF THE URINE.

ORGANIC SUBSTANCES—INORGANIC SUBSTANCES—ORGANIZED SUBSTANCES.

Classification of Albumens—Properties of Albumen—Coagulation by Heat—Coagulation by Nitric Acid—Tests for Albumen—Fallacies in Heat Test—The Nitric Acid Test—Fallacies in Nitric Acid Test—Tanret's Reagent—Picric Acid Test—Ferrocyanide of Potassium Test—Nitro-prussiate of Soda Test—Sodium Tungstate Test—Spiegler's Test—Stutz's Test—Roch's Test—Jaworowski's Test—Other Tests for Albumen—Mixed Albuminuria—Relative Value and Delicacy of Various Albumen Tests—Quantitative Analysis—Process of Tanret and Troyes—Bödeker's Method—Process of Brandberg—Esbach's Process—Zahor's Method—Pathological Significance—Therapeutic Indications—Purulent Albuminous Urine—Globuline—Qualitative and Quantitative Analysis—Process of Hammarstein—Pathological Significance—Fibrine—Mucine—Properties of Mucus—Analysis—Leucomaines and Ptomaines—Peptones—Properties of Peptones—Analysis—Process of Hofmeister—Reaction with Tanret's Solution—Other Reactions—Pathological Significance—Hemi-albumose—Properties—Analysis—Transitory Albuminuria—Pathological Significance.

THE abnormal constituents of the urine may be considered as consisting of three groups, viz.: (1) **Elements of an Organic Nature**; (2) **Elements of a Mineral or Inorganic Nature**; and (3) **Organized Substances**.

ORGANIC SUBSTANCES.

Albumen.
 Peptones.
 Glucose.
 Levulose.
 Lactose.
 Inosite.
 Cystine.
 Tyrosine.
 Leucine.
 Acetone.
 Melanine.
 Diverse acids.
 Bile elements.
 Fatty matter.
 Tube-casts.

INORGANIC SUBSTANCES.

Salts of ammonia (carbonate of ammonia, ammonio - phosphate of magnesia, urate of ammonia).
 Sulphuretted hydrogen.

ORGANIZED SUBSTANCES.

Blood corpuscles (hæmoglobine).
 Leucocytes (pus).
 Mucus.
 Epithelial cells.
 Spermatozoa.
 Infusoria.

Organic Substances.

ALBUMEN.

$C_{36}H_{56}N_9O_{11}S$ (Lieberkhün).

Carbon	53 per cent.
Hydrogen...	7 „
Nitrogen	15.50 „
Oxygen	23 „
Sulphur	1.50 „
				<hr/> 100.00

Albumen is primarily synthetically formed by plants. It is introduced into the animal organism as food, and there undergoes important and varied modifications before being incorporated with, and forming part of, the living tissue. It exists in greatest abundance in blood-plasma. It likewise forms an important constituent of lymph and chyle, of serous fluids, and of the other textures of the body. It exists in large quantity in the egg, and this form of albumen is usually regarded as the standard of albuminous substances, other forms of albumen being classed in the degree of their constituent relationship to this variety. Other proteids exist in animal tissues, which have

important relations to the pathology and diagnosis of disease. The entire group may be thus classified :

Class I.—NATIVE ALBUMEN	...	{	1. Egg albumen.
		}	2. Serum albumen.
Class II.—DERIVED ALBUMENS		{	1. Acid albumen or syntonin.
		}	2. Alkali albumen.
		}	3. Casein.
Class III.—GLOBULINS	...	{	1. Globulin (crystallin).
		}	2. Paraglobulin (fibrinoplastin, serum globulin).
		}	3. Fibrinogen.
		}	4. Myosin.
		}	5. Vitallin.
Class IV.—FIBRIN		{	Mucin.
Class V.—COAGULATED PROTEIDS		{	Leucomaines, Ptomaines.
Class VI.—PEPTONES...	...	{	Parapeptone-Hemialbu-
		}	mose or Propeptone.
Class VII.—LARDACEIN OR AMYLOID SUBSTANCES.*			

According to Hoppe-Seyler, the composition of the foregoing varies from C 51·5, H 6·9, N 15·2, S 0·3, O 20·9 to C 54·5, H 7·3, N 17·0, S 20, O 23·5.

Properties of Albumen.—Albumen exists in a soluble and in an insoluble form. In the former condition it exists in all the fluids and tissues of the body, and in vegetables. It is convertible into the latter form by boiling with water, by absolute alcohol, acids, and strong alkalies. On incineration it evolves nitrogen; and heated in a tube with caustic potash, ammonia is given off, which may be recognised by its action on litmus paper, and the formation of white fumes on coming in contact with hydrochloric acid. Dried, it forms as an inodorous, insipid, and slightly yellow amorphous substance, soluble in water, but insoluble in alcohol.

The presence of sulphur in albumen may be thus demonstrated. Boil albumen with a solution of caustic soda. A sulphide of soda is formed which gives a black precipitate with a salt of lead, or

* For detailed relations of the foregoing the reader is referred to special works.

by calcining a quantity of albumen with caustic potash and nitrate of potash in a porcelain crucible, a sulphate of potash is produced, easily recognised by the action of chloride of barium. From an aqueous solution albumen is precipitated by alcohol, which, according to the nature of the precipitate, may be redissolved in whole or in part. Albumen is coagulated by all the mineral acids with the exception of ortho- and pyrophosphoric acid. It is coagulated without combination by carbolic acid, picric acid, nitric acid, sulphuric acid, and tannic acid. Concentrated hydrochloric acid, especially with the addition of a little sulphuric acid, dissolves a small portion of the albumen, and imparts to the remainder an intense blue colour which persists a long time. Nitric acid causes serum-albumen to become yellow, and on the addition of ammonia a deep orange colour is the result. This is the *xantho-proteic reaction*.

A solution of mercurous and mercuric nitrates, made by dissolving one part of mercury in two parts of nitric acid and four parts of water, imparts a deep-red colour to albumen in either the solid or liquid form when the mixture is warmed from 60° to 100° Cent. (Millon's reaction). As a test, this is not applicable to the urine, as four different precipitates are formed by it. Bichloride of mercury readily precipitates albumen from solution, the precipitate being soluble in an excess of albumen. It is likewise precipitated by nitrate of silver, acetate of lead, tannin, creosote, aniline, etc. It is not precipitated by formic acid, tartaric acid, nor acetic acid, the last of which separates proteine. Potash, soda, and the carbonates of these bases dissolve albumen, and prevent its coagulation by heat.

Sulphuric ether coagulates egg albumen. The albumen of the serum is not so coagulated.

Coagulation of Albumen by Heat.—If a solution of albumen, neutral or acid, be heated to a temperature of 62° Cent. (94° Fahr.), it begins to become cloudy owing to the separation of albumen; at a temperature of 72° to 75° Cent. (104° to 107° Fahr.) the coagulation is complete. The more dilute the solution of albumen, the higher is the temperature required. The precipitate thus formed is insoluble in water or in a moderate quantity of nitric acid. The point of coagulation by heat is modified

by certain acid salts and some alkalies. Thus, sulphate of magnesia and sulphate of soda have *per se* no effect upon albumen, but when the albuminous solution is saturated by them, the point of coagulation is lowered to 50° Cent. (82° Fahr.). It is important to keep this in view in testing for very minute quantities of albumen. Should the albuminous solution be alkaline, and especially if the quantity of albumen be small, coagulation on heating does not take place. It is, therefore, indispensable, under such circumstances, previously to acidulate the urine, or at least to render it neutral, and for this purpose it is necessary to employ an acid which does not coagulate albumen, such as acetic acid. When the urine is alkaline, the acetic acid must be sparingly added, otherwise the albumen is *not* precipitated by heat. Sulphate of soda added to a solution of albumen, acidified by acetic acid, gives a precipitate of albumen on heating. Traces of albumen may thus be detected by saturating the urine with sulphate of soda, acidifying with acetic acid, filtering, and heating in a test-tube. It is important to note that urine containing semen, acidulated with acetic acid, gives a precipitate on being heated, the precipitate dissolving on the addition of an excess of the acid.

Coagulation of Albumen by Nitric Acid.—Nitric acid coagulates albumen without combining with it. If it be added drop by drop to albuminous urine, a white cloud of albuminous substance is the result, which disappears on agitation. *If in excess the precipitate is redissolved.* If about a tenth or a fifth of the volume of urine be added of the acid, a copious and persistent white precipitate is the result. This precipitate partakes sometimes of a colour derived from the oxidation—a pink colour—of uroerythrine, and sometimes, though rarely, of indigo.

Tests for Albumen in the Urine.

Coagulation of Albumen by Heat.—At a temperature of from 60° to 100° Cent. albumen contained in urine is coagulated. To ensure the greatest possible accuracy in testing for albumen by means of heat, the following precautions should be observed: The urine should be that passed after breakfast, as frequently

the urine passed after resting and abstinence from food is free from albumen, while containing it after food and exercise. If the urine be acid, as it naturally is, it is not necessary to acidulate it; but if it be alkaline, *just sufficient* acetic acid should be added to render it acid. In order to separate globulin, chloride of sodium or sulphate of magnesia should be added, and the urine filtered. A test-tube is then half filled with the clear urine, and the fluid is to be freely boiled. If albumen be present, and the circumstances of light, etc., favourable, the characteristic flaky albuminous precipitate is easily recognised. It is better to boil simply the upper stratum of the fluid, as in this manner the contrast between the two portions, especially against a dark background, reveals the smallest trace. This precipitate is unaffected by a small quantity of acetic or nitric acid, *but is redissolved* by an excess of them.

Fallacies in the Heat Test.—A modification of albumen is met with occasionally which is not coagulated by heat.* Certain important precautions have to be observed in the treating of albuminous urine with acetic acid, in order to obtain a satisfactory precipitate by means of heat. If more acetic acid be added than is necessary to neutralize the free alkali and slightly acidulate the fluid, boiling may produce a mere cloudiness. If more acid be then added, and the urine boiled, it becomes perfectly clear. If at first the acid be added in considerable quantity—for instance, to the extent of about a fourth—the fluid is unaffected by boiling, and *then* the addition of nitric acid does *not* cause precipitation of the albumen.

Alkaline albuminous urine is not precipitated by heat, but the subsequent addition to it of nitric acid causes a precipitate of albumen. In alkaline urine the albumen exists as an albuminate of potash. Phosphates of lime or magnesia are thrown down by heat, and turbidity results from the escape of carbonic acid. This precipitate is distinguishable from albumen by being immediately dissolved by the addition of a few drops of acetic or nitric acid. Albuminous urine to which a drop or two of nitric acid may have been added accidentally, or purposely for the sake

* Annal. des Malad. des Organ. Genit. Urin., 1888, p. 213, and *Ibid.*, 1889, p. 703.

of experiment, is not coagulated by heat. In this case the albumen had been converted into a nitrate of albumen.

Urine containing pus is necessarily coagulated by heat. Urine containing mucin is not coagulated by heat, but the addition of acetic acid precipitates the mucin. Acetic acid also throws down cystin, and uric acid when in excess.

The Nitric Acid Test.—In proceeding to test for albumen in urine by means of nitric acid, the urine should be rendered slightly acid by means of a few drops of acetic acid, and filtered. Cystin and mucin, if present, are thus separated. Two or three drachms of the filtered solution are then placed in a conical glass or test-tube. By means of a pipette, a small quantity of pure, colourless nitric acid is allowed to trickle down on the side of the glass, and thus mingle with the urine. The acid, having a higher specific gravity, passes under the urine, and at the junction of the two fluids a sharp white band or zone forms, varying in size with the quantity of albumen present. The acid may be first placed in the glass, and the urine subsequently added, but the result is identical. The precipitate of albumen formed by the first few drops of acid is redissolved on shaking the fluid, but reappears and increases by further addition of acid, and does *not* disappear on being heated. Should the precipitate disappear on heating, it would be due to uric acid, urea, copaiba, etc. Not more than from a tenth to a fifth of nitric acid should be added to the urine.

If the urine be rich in colouring matter, as in fever, at the line of junction of the fluids certain shades of colour may be formed, a red colour resulting from the presence of uroerythrine, a blue due to indigo, a rose-red to indican, a brownish-red to blood colouring matter, and a green to undecomposed biliary constituents. The albumen itself partakes to a greater or less degree of these colours, according to circumstances.

Fallacies in the Application of the Nitric Acid Test.—With urine rich in urea, such as that of the dog, nitric acid gives a precipitate of nitrate of urea, which is much less soluble than urea, especially in acid solutions. The precipitate is distinguished from albumen by its crystalline form, by its solubility on the addition of a small quantity of water, by the fact that more or

less effervescence takes place when the nitric acid is added, arising from the partial decomposition of urea, that it is readily dissolved by heat, and, finally, that it forms higher up in the tube than the line of contact of the two liquids, and that the precipitate does not appear until after the lapse of a considerable interval. It first appears as a thin layer on the surface, and gradually thickens and extends from above downwards.

Urates are decomposed by the addition of nitric acid, and a precipitate of uric acid is thus caused, which may be mistaken for albumen owing to its amorphous appearance. Slight heating causes the uric acid to disappear; and on operating on a fresh specimen of urine, a precipitate is found to be occasioned by acids which do *not* coagulate albumen, such as phosphoric and acetic acid.

If the urine contain a large quantity of carbonic acid, as arising from alkaline decomposition, and either in a free state or combined with ammonia, or potassium, or sodium, as from the administration of alkaline carbonates, or salts of the vegetable acids, such as citrates, tartrates, malates, etc., the addition of nitric acid causes its liberation with effervescence. While under ordinary circumstances this does not interfere with the nitric acid test, it may so happen, as when, for instance, the quantity of carbonate of ammonia is very large, that the effervescence is such as completely to nullify the test. Again, in such a case, the amount of acetic acid necessary to neutralize and acidify is so large as permanently to hold the albumen in solution. Alkaline urines are always more or less opaque, owing to the presence of amorphous phosphates and bacteria, and cannot be sufficiently cleared by filtration. To obviate this difficulty, Hoffmann and Ultzmann recommend the following process: To the urine add about a fourth of its volume of liquor potassæ; warm the mixture and filter. Should the filtrate be not quite clear, a few drops of the following solution should be added: magnesium sulphate and ammonium chloride of each one part, distilled water eight parts, and pure liquor ammoniæ one part. The fluid thus becomes clear, and the presence of albumen may be demonstrated by the use of acetic and nitric acid, or the ferrocyanide of potassium test. When the urine contains *resinous substances*,

such as copaiba or turpentine, the addition of nitric acid determines a yellowish-white precipitate, which is dissolved by heating and excess of nitric acid. This substance is distinguished from albumen by its characteristic odour, by its solubility in alcohol, and by the fact that it is not precipitable by heat. If the urine be previously heated, the nitric acid does not precipitate the resin.

Tanret's Reagent.—The double iodide of potassium and mercury, prepared as under, has been recommended by M. Tanret, of Paris, as a delicate test for albumen :

Iodide of potassium	3.32 gr.
Bichloride of mercury	1.35 gr.
Acetic acid	20 c.c.
Distilled water, q.s. ad	64 c.c.

This test is employed in the ordinary manner, and is one of extreme sensibility. A weighty objection to it is that it precipitates alkaloids in the urine, and albumen, or some other albuminous substance, apart from any morbid process or manifestation of ill-health. Thus, M. Chateaubourg, in 701 examinations of the urine of healthy persons, found 'albuminuria' in no less than 592 instances, employing this test ; and Dr. Dickinson, in every one of 100 consecutive cases which presented themselves in hospital and private practice, in many of which 'there was no reason to doubt that the urine was absolutely natural.' Tanret's solution likewise causes a cloudiness in the urine when urates exist in excess. This disappears on heating, to reappear on cooling. If the urine be *previously heated*, Tanret's solution does not precipitate the urates. It precipitates peptones and globuline in the urine, and is a more delicate test for these than picric acid, but, unlike the precipitate with picric acid, that with mercuric iodide is not dissolved on the application of heat. Jaccoud* gives the following caution regarding Tanret's solution : 'I insist the more readily on the causes of error arising from the employment of Tanret's solution, seeing that it is so much used in France, and that I have been long struck with its drawbacks. It is too powerful or too delicate. It precipitates many other principles besides true albumen or serine, and I cannot help

* *Clinique Médical*, 1886.

observing that it has been since its vulgarization (in France) that albuminuria in the apparently healthy has been so frequently discovered. Possessing the property of coagulating all proteic substances (not to speak of alkaloids), I am convinced that many of those cases presented, in reality, nothing in common with true albuminuria or serinuria. From this point of view, nitric acid and heat are the most certain reagents. Remove the globuline with sulphate of magnesia, filter, and treat the filtrate with heat and nitric acid or the acetic solution of ferrocyanide of potassium. If a precipitate result, it is certain to be one of serum albumen. The same fluid, treated by Tanret's solution, is as likely to give a precipitate of peptones as albumen.' The precipitate which Tanret's solution gives with albumen *is not dissolved* on heating. It is also insoluble in alcohol. It is thus distinguished from peptones and alkaloids.

Picric Acid Test.—Picric acid was first suggested as an albumen test by M. Gallipe. A saturated solution of this acid added to urine is a delicate test for albumen. Such solution is slightly heavier than distilled water, so that, unlike nitric acid, it has a tendency to float on the surface of the urine. When the urine is alkaline, the addition of a drop or two of acetic acid renders the test more delicate. The precipitate so formed is insoluble by boiling. The coagulum formed with picric acid in cold urine requires a large excess of water for its solution. It is readily dissolved by caustic potash and ammonia, so that if the urine be alkaline, it should be acidified, or rendered neutral, before applying the test.

The objections to the picric acid test are the following: It throws down creatinine, copaiba, peptones, mucin, quinine, cinchonidine, morphia, atropia, and most other vegetable alkaloids; but these precipitates, unlike that caused by albumen, disappear on the application of heat, and reappear as a cloud on cooling. On microscopic examination, as pointed out by Dr. George Johnson, the peptones present a homogeneous appearance, and are free from solid particles, while the precipitate of the vegetable alkaloids is finely granular. When peptones which have been dissolved by heat are precipitated on cooling, they contain, as Dr. Johnson remarks, exceedingly minute granules, which are

incessantly dancing about with so-called 'Brownian movement.' The same authority states that 'there is no known substance occurring in either normal or abnormal urine, except albumen, which gives a precipitate with picric acid insoluble by the subsequent application of heat. This is incorrect. Urine containing semen gives a precipitate with picric acid solution practically unaffected by heat. While the fluid is still warm the addition of a little nitric acid renders it quite transparent, and the *transpareney is permanent*. If to the same urine before boiling nitric acid be added, after the precipitation by picric solution, the precipitate is dissolved, and the fluid becomes transparent, but *the transpareney soon passes off*.'

Uric acid is precipitated from normal urine by picric acid.* I have observed that the precipitate is very like albumen in appearance, and disappears on boiling, the fluid assuming a beautiful pink colour. This applies to urine containing potash in excess. In the case of urine containing an excess of urate of ammonia, the addition of picric acid, and exposure to air for a little time, causes the urine to assume a deep port-wine colour, but in my experience *no* precipitate. The deposit most readily and abundantly forms when the acid is employed in the form of fine powder, instead of the aqueous solution. Under the microscope the deposit appears as fine, needle-like processes, in the form of stars, and of more or less irregular prismatic crystals. Acted on by boiling water, part of the precipitate forms a combination of creatinine with picrate of potassium.

In using the aceto-picric test, or Tanret's solution and heat, according as the urine is rich in albumen, it appears in two forms. When but a small quantity of albumen is present, a mere cloud is produced, and this Professor Bouchard has proposed to term the *non-retractile form* of albumen. When present in larger quantity, distinct flakes are formed, termed by the same authority the *retractile form*.

Dr. Dickinson considers the picric acid and the mercuric iodide tests as not sufficiently discriminating.

Ferrocyanide of Potassium Test.—A solution of ferrocyanide of potassium acidulated with acetic acid forms a delicate test for

* *Zeit. für Physiol. Chem.*, 1886, p. 39.

albumen. A preliminary objection to the use of all tests requiring acidulation by acetic, citric, or lactic acid is, that by either of these mucin is thrown down, and such acidulated tests are unsuitable for urines containing a small quantity of albumen. For ordinary purposes in practice, Dr. Pavy has suggested a most convenient contrivance for the application of this test; pellets containing a sufficient quantity of citric acid and ferrocyanide of potassium being formed and enclosed in an indiarubber capsule.* These are carried about in a small tube, and as no heat is required in testing with them, they are of easy application. Dr. Pavy's directions are as follows: About a drachm of urine is taken, an acid pellet is dropped into it, which a little agitation quickly dissolves. One of the ferrocyanide pellets is next dropped in, and the urine again shaken to facilitate solution. If albumen be present, a precipitate immediately occurs. Should the urine contain urates, it is to be clarified by heating. On the addition of the acid pellet alone a precipitate is sometimes formed, and this precipitate may be due either to mucin or to uric acid. In the latter case, dilution of the urine with an equal bulk of water prevents the appearance of the precipitate; in the former case, the precipitate with both the acid and the ferrocyanide pellet should be compared with that resulting from the acid alone.

A concentrated solution of ferrocyanide of potassium with acetic acid is, according to Hofmeister, the most delicate of all the albumen tests, and it precipitates all the albuminous bodies, but not peptones. Salkowski states that this test fails when a large amount of chloride of sodium is present, but the urine never contains this element in such quantity as to prevent the precipitation of albumen.

Dr. Zouchlos recommends the following as convenient bedside tests for albumen in the urine: 1. Some drops of a mixture of 1 part of acetic acid and 6 parts of a 1 per cent. solution of sublimate, when added to urine containing albumen, produce a slight cloudiness. Peptone, when mixed with acetic acid and sublimate in the above-mentioned proportions, causes no cloudiness, and

* These pellets may be obtained from Mr. Cooper, 66, Oxford Street, London.

this is true also of uric acid, solution of urea, phosphates and sugar. When the urine is much concentrated, it does not become cloudy on the addition of sublimate and acetic acid.

2. Another method which is still more exact—even more so than that with the ferrocyanide of potassium and acetic acid—is the method with rhodanide of potassium and acetic acid in the cold. It is best to mix 100 c.c. of a 10 per cent. solution with 20 c.c. of acetic acid, and to add some drops of this mixture to the urine to be tested. When albumen is present in small quantities, a distinct cloudiness occurs immediately on the addition of the above-mentioned mixture; when the amount of albumen is large, a thick white precipitate is thrown down. An excess of the fluid does no harm. Normal urine, when thus tested, invariably gives a negative result. The most convenient method is that with rhodanide of potassium and succinic acid, which can be carried about in the solid form in boxes. Equal parts of succinic acid and rhodanide of potassium are mixed together, and a small quantity is added to the urine. If even the smallest amount of albumen is present, cloudiness is produced.

Nitroprussiate of Soda Test.—M. G. Nya* recommends a solution of nitroprussiate of soda as a test for albumen. It is to be employed in the same manner as ferrocyanide of potassium; that is to say, before a solution of the reagent is added to the suspected urine, it must be previously acidulated by acetic acid. When precipitation of urates occurs, the urine must be clarified by heating. The nitroprussiate solution must be protected from light in order to prevent decomposition.

Sodium Tungstate Test.—We are indebted to F. L. Sommenschein† for the recommendation of sodium tungstate as an albumen test.‡ The solution of this salt must be acidulated with acetic or phosphoric acid. It precipitates peptones, acid urates, and mucin. In combination with strong acetic acid, sodium tungstate is a more delicate albumen test than with citric acid. With the latter it gives a marked mucin reaction.

* *Med. Chir. Rundschau*, 1887, and *Archiv der Pharm.* xxv., 1887.

† *Journal of the Chemical Society*, March, 1874.

‡ Also as a delicate test for blood, producing, with ammonia, a green colour when blood is so diluted as not to be recognisable by the spectroscope.

Spiegler's Test.*—According to Spiegler, the following reaction discovers albumen when it exists in the urine in so small a proportion as 1 part in 250,000: Corrosive sublimate 8 parts, tartaric acid 4 parts, distilled water 200 parts, glycerine 20 parts. A test-tube is filled to a third of its capacity with the reagent, to which a few drops of acetic acid have been added, by pouring along the tube wall, and the urine carefully added. When albumen exists, an opaque ring forms at the junction of the fluids. Should the urine at the same time contain iodine, the albuminous ring becomes of a yellow colour, the iodine yellow dissolving in alcohol. The added acetic acid separates almost all the mucin. With this reagent, Spiegler has been able to detect transitory albuminuria in from twelve to twenty-four hours after physical or intellectual exertion.

Stutz's Test.—This consists of a mixture of bichloride of mercury, chloride of sodium, and citric acid. Added to albuminous urine, this solution causes an abundant precipitate of albuminate of mercury. It is to be noted that it likewise precipitates uric acid in urines rich in this acid, and, therefore, in employing the test, the urine should be diluted with an equal quantity of water.

Jaworowski (*Wiadomosci Farmaceutyczne*, June, 1892) suggests, as a most delicate test for albumen, 1 part of molybdate of ammonia with 40 parts of water and 5 parts of tartaric acid. The presence of $\frac{1}{300000}$ of albumen is thus revealed. The urine must be limpid and acid. If necessary, it may be acidified with tartaric acid. The albumen may be completely removed by gradual addition of the reagent and filtration. An excess dissolves the albumen.

Roch's Test—Sulphosalicylic Acid.—This acid, which is obtained by the action of sulphuric acid on salicylic acid, has been recommended as a most sensitive albumen test by M. Roch. When the acid is added to an albuminous solution, a white precipitate possessing an acid reaction results, which, on being treated with perchloride of iron, gives an intense red coloration characteristic of sulphosalicylic acid. The compound

* 'Über eine empfindliche Reaktion auf Eiweiss im Harn,' etc. (*Centralblatt f. Klin. Medic.*, 1893, No. 3, p. 49).

thus formed with albumen is insoluble, and resembles that obtained with metaphosphoric acid. The whole of the albumen is precipitated, and 0·0005 gramme of albumen may be thus detected in 10 c.c. of albuminous urine. In employing the test a few crystals of sulphosalicylic acid are to be added to a small quantity of urine and the fluid shaken. The presence of albumen is revealed as above. The reaction is not interfered with by the presence of urea, uric acid, peptones, sugar or other substances. (*Archiv der Pharmacie*, xxvii., 1889, 998; and *L'Orose*, xi., December, 1889, 413.)

Other Tests for Albumen.—Of the other tests for albumen may be mentioned *acidulated brine*, first suggested by Sir William Roberts, and since abandoned by him; alcohol, which, while it precipitates albumen, also coagulates mucus, and renders certain salts insoluble; tannin, which also precipitates mucus, and other animal substances which the urine contains; alum, which determines precipitates in urine not albuminous; corrosive sublimate, which seldom fails to precipitate urine whether it contains albumen or not, being decomposed by the sulphates, phosphates, and the organic matter in the urine; carbolic acid, and Tidy's test, which consists of equal parts of carbolic and acetic acids, and acetate of uranium; acetic acid, with sulphate or chloride of sodium (Panum, Heynsius); trichloroacetic acid (Raabe); Millon's reagent; biuret reaction; reaction of Adamkiewicz. Urine containing albumen, on being shaken, retains its froth for an indefinite period, sometimes for days. These tests are much less trustworthy than those described in detail, and do not merit further consideration.*

Mixed Albuminuria.—Blood normally contains two coagulable albuminous substances, viz.: serum-albumen (serine) and globulin. In the majority of instances in which serum-albumen is found in the urine, globulin coexists with it. In a small number of instances, it sometimes happens that but one of these constituents is found, and thus we may have a pure case of *serinuria* or *globinuria*. Globulin is a more diffusible substance

* Dr. Oliver, of Harrogate, has applied most of these tests to clinical purposes in the form of test-papers, after the manner first suggested by Professor de Luna, of Madrid (*Lancet*, October 14, 1882).

than serum-albumen, and when but one of these bodies exists, it is more likely to be globulin. When albumen reaches the stomach it is coagulated, and in this form insoluble in water. Here it is acted upon by the gastric juice, dissolved, and converted into peptone, though in this condition but slight traces of it are found in the blood; yet, as with urea, uric acid, and kreatin, the kidney separates it from the blood, and it may exist in large quantity in the urine, constituting peptonuria. The conversion of albumen into peptone is by successive stages, and hence intermediate products may find their way into the blood, and ultimately into the urine. The most important of these compounds is hemi-albumose, or propeptone. According to Senator, the occurrence of propeptone in the urine is by no means a rare occurrence. Cases occasionally occur in which propeptone, serum-albumen, and globulin occur simultaneously in the urine, and to such the term 'mixed albuminuria' specially applies.

Globulin is precipitated by sulphate of magnesia; propeptone is not precipitated from its watery solution by boiling, but is precipitated in the cold state by acetic acid, and ferrocyanide of potassium, nitric acid, acetic acid, and a concentrated solution of chloride of sodium. Peptones are not precipitated by heat, nitric acid, nor the ferrocyanide test, but are precipitated by picric acid, the precipitate disappearing on the application of heat, to reappear on cooling, and by the mercuric-iodide and tungstate tests, the precipitant similarly disappearing and re-appearing. Fehling's solution, it may here be remarked, though in anticipation, gives a characteristic rose or pink-tinted colour with peptones.

In all cases in which there is doubt as to the presence of propeptone, peptones, and albumen existing simultaneously in the urine, the following procedure should be adopted: (1) Acidify the urine with acetic acid, and then carefully add a concentrated solution of ferrocyanide of potassium. All the albuminous bodies are thus precipitated, but not peptones. (2) Add carefully a little nitric acid to the non-warmed urine, and if cloudiness result, boil the urine. If the precipitate then partially or entirely disappear, the presence of propeptone is indicated. (3) A concentrated solution of chloride of sodium or sulphate of

magnesia added to urine acidulated with acetic acid or nitric acid gives a precipitate which disappears on heating; then pro-peptone is likewise indicated. Mucin is precipitated by citric or acetic acid, and may be removed by filtration.

Hindenlang* recommends metaphosphoric acid as a delicate test for albumen, but it likewise precipitates peptones. A precipitate caused by this acid, but *not* by acetic acid and ferrocyanide solution, in the original urine, would indicate peptone to the exclusion of other substances. Should the urine give a precipitate with these two reagents, then by boiling and filtering the serum-albumen and globulin may be separated. The filtrate should not give a precipitate with acetic acid and ferrocyanide of potassium; but if peptone be present, a precipitate would be given with metaphosphoric acid.

Relative Value and Delicacy of the Various Albumen Tests.—In view of the pathological importance which attaches to the early detection of albumen in the urine, and the vast number of details which fall to be, or are supposed to be, remembered by the student, it is not desirable that equivocal albumen tests should be indefinitely multiplied, but rather, from the practical point of view, that the relative delicacy and consequent value of the best known of them should be determined. The following table exhibits the result of careful experiments undertaken by me for this purpose.

* *Berlin Klinik Wochenschrift*, 1881, No. 15.

Quantity of albumen in 1,000 grms. of urine.	Tanret's solution, the urine poured drop by drop on it.	Saturated solution of picric acid.	Saturated solution of picric acid with citric acid.	Nitric acid, Heller's method.	Coagulation by heat.	Ferrocyanide of potassium with acetic acid.*	Solution of sodium tungstate with acetic acid.	Solution of sodium tungstate with citric acid.
0.50 gr.	A distinct precipitate, which settles and becomes flocculent on repose.	A distinct opaque yellowish precipitate floating on the clear fluid underneath.	An abundant albumen precipitate of yellowish colour, occupying greater part of tube.	Well-marked albumen precipitate; flocculent and settling on repose.	Well-marked albumen precipitate at boiling point.	Distinct supernatant albumen precipitate, semi-transparent.	Copious and well-marked albumen precipitate.	Well-marked instantaneous albumen precipitate.
0.25 gr.	Marked albumen reaction; precipitate flocculent and separating on repose.	Distinctly marked albumen reaction; yellowish supernatant precipitate.	Well-marked floating yellowish precipitate.	Well-marked albumen reaction; more distinct on repose.	Distinct albumen precipitate at boiling point; less opaque.	Albumen precipitate; more transparent, milky.	Well-marked albumen precipitate, clear supernatant disc.	Distinct albumen reaction; precipitate floating.
0.12-25 gr.	Marked albumen reaction at boiling point.	Yellowish supernatant albumen; precipitate more transparent.	Well-marked floating yellowish precipitate, less dense.	Distinct precipitate; marked on repose.	Distinct precipitate at boiling point; less copious.	No appreciable result.	Distinct precipitate against clear supernatant disc.	Appreciable precipitate. Not nearly so distinct as in combination with acetic acid.
0.06 gr.	Distinct albumen reaction at boiling point.	Marked yellow albumen reaction.	Distinct supernatant yellow precipitate.†	Distinct precipitate, but only after an interval of 10 minutes.	Appreciable precipitate at boiling point.	No result.	Distinct precipitate against supernatant fluid.	Appreciable precipitate.
0.03 gr.	Distinct albumen reaction at boiling point. More distinct than 'Tanret' alone.	Very faint yellowish precipitate.	Very faint yellowish precipitate.‡	Distinct albumen reaction after an interval of 15 minutes.	Appreciable albumen reaction at boiling point.	—	No reliable precipitate.	No reliable precipitate.
0.015 gr.	Appreciable albumen reaction.	Albumen reaction slight.	Albumen reaction.‡	Albumen reaction after 15 minutes.	Albumen reaction at boiling point.	—	—	—
0.007 gr.	Albumen reaction, but less marked than by No. 1. process.	No appreciable reaction.	No appreciable reaction.	Faint albumen reaction after 1 hour.	Albumen reaction at boiling point.	—	—	—
0.0035 gr.	Negative result.	—	—	No reliable result.	Faintest possible reaction at boiling point.	—	—	—

* The combination of acetic acid with potassium ferrocyanide forms a more delicate test.
 † Acetic acid more delicate than citric acid combination. ‡ *Ibid.*

The conclusions which these experiments impress upon me are: That the delicacy of the best albumen tests stands in the following order: Tanret's solution (open to the objections mentioned above), heat, nitric acid, and aceto-picric solution.

The foregoing table further shows (a result which is at variance with the statement of Hofmeister) that ferrocyanide of potassium with acetic acid proved in my hands the least delicate of the tests employed, ceasing to give any result with 1 part in 8,333; that tungstate of soda with citric acid is less delicate than with acetic acid, the latter ceasing to give a precipitate at 1 part in 33,333; that the aceto-picric solution ceases to give a reaction at 1 part in 148,857·5, but gives a reaction at 1 part in 66,666. Sir William Roberts states that, in his hands, the picric acid tests gave a faint reaction in a watery solution containing 1 part in 100,000. I have been unable to confirm this.*

Quantitative Analysis.—The most accurate, though certainly the most troublesome, method of determining the amount of albumen in solution in any fluid, is that by weighing. For this purpose coagulation is necessary, and this may be accomplished either by boiling the urine, or by coagulating the albumen by a chemical agent, filtering, collecting, and then weighing. If the former process be adopted, a certain quantity of urine is taken,

* With reference to the heat test, Sir William Roberts ('Discussion on Albuminuria' at Glasgow Pathological and Clinical Society, 1884) remarked: 'I gauged the delicacy of the test in the following manner: A moderately albuminous urine was diluted with 2,000 times its bulk of water. I could with certainty detect the presence of albumen in this dilution by the boiling test. Now, the urine operated on was found, on a careful weighing analysis, to contain 0·76 per cent of dry albumen. If you work out the sum which these figures furnish, you will get the astonishing result that the boiling test, with due acidulation, enables you to detect albumen in a watery solution which contains only one part in 250,000.' Sir William Roberts's calculation is slightly wrong. His data give one part in 263,158.

Professor Grainger Stewart (*Edin. Med. Jour.*, May, 1887) states it as his opinion that picric acid is the most delicate of all the reagents which we possess for albumen, the potassio-mercuric iodide ranking next to it; while Dr. Unger Vetlesen, of Christiania, believes the relative delicacy to be represented by the following figures: Heller's test, 85; trichloroacetic acid, 82; ferroc. potass. and acid. acet., 82; metaphosphoric acid, 72; picric acid in solution, 36; Glauber's salt and acetic acid, 25.

from 50 to 150 grammes being a convenient amount; a few drops of acetic acid are added to it, so as to render it distinctly acid, and it is then filtered. According as the urine is rich in albumen, the filtration will be slowly accomplished. If rich in albumen, water should be added, so that from 25 to 100 cubic centimetres of the solution should contain from 0.30 gr. to 0.50 gr. of dried albumen, as judged by the qualitative analysis. The diluted urine is then put into a porcelain capsule, and gradually heated to ebullition, the fluid being stirred by means of a glass rod. The boiling should be continued from a quarter to half a minute, and the fluid then passed through a filter, whose weight has been previously determined. Filtration takes place rapidly; the capsule is then washed with distilled water, the adherent particles of the precipitate being detached, and the fluid and the remaining precipitate is again thrown on the filter. Then, by means of a pipette containing boiling distilled water, the albuminous precipitate is washed, the jet being directed so as to convey the albumen towards the cone of the filter. The washing is to be continued until the albumen becomes perfectly white. The washing removes the chlorides from the albumen. Sometimes it is necessary to use hot alcohol for the purpose of washing. The filter and contents are now carefully placed in a stove, and exposed to a temperature of 100°C. Desiccation takes from five to six hours, and the mass must be so arranged as to facilitate this. The desiccation is known to be complete when two weighings at an interval of from half an hour to an hour, in the stove, give an identical weight. From the whole weight that of the filter is to be subtracted, and the difference represents the weight of the albumen.

Two sources of error in this process are to be noted. In the first place, the albumen which passes into the urine is identical with that of the serum of the blood; it contains serine and dissolved fibrine. In the second place, the albumen retains always more or less of the colouring matter of the blood, and phosphates of lime and magnesia, especially if acetic acid has not been added. To obviate the former source of error, the albumen should be washed with alcohol, and to avoid the latter, the dried albumen should be incinerated, and the weight of the ash deducted. These

sources of error are, however, so insignificant as to be clinically unimportant.

Coagulation of Albumen by Carbolic Acid—Process of Méhu.—To the albuminous urine two or three drops of acetic acid are to be added, and the fluid filtered; 100 c.c. of the filtrate are then taken, and 2 c.c. of ordinary nitric acid are added, with 10 c.c. of the following solution :

Crystallized carbolic acid	10 grammes
Commercial acetic acid	10 „
Alcohol (90°C.)	20 „

The mixture being shaken, the albumen immediately coagulates, and the whole is thrown on a filter. Filtration takes place so rapidly that the uric acid is almost entirely found in the filtered fluid, where it gradually crystallizes. The albumen collected on the filter is washed with boiling water containing 1 per cent. of carbolic acid, and is then dried towards a temperature of 105° F. or C.; any excess of carbolic acid, being volatile, disappears with the water.

If the urine be rich in albumen, a preliminary experiment is made with from 25 to 30 c.c. It should be diluted with water, so that the volume will amount to 100 c.c.

This process is not affected by the presence of sugar or such mineral substances as chloride of sodium, nitrate of potash, iodide of potassium, sulphate of magnesia, and ammoniacal carbonates. When the urine contains carbonate of ammonia, the precipitate has a creamy appearance.

Process of Tanret and Troyes.—Tanret and Troyes have recommended, for the volumetric estimation of albumen, its precipitation by a double iodide of mercury and potassium. For the precipitating solution the formula is: Potass. iodide 3·22 grammes, hydrarg. bichlor. 1·35 gramme, aq. destillat. ad 100 c.c. For the confirmatory solution: Hydrarg. bichlor. 1 gramme, aq. destill. ad 100 c.c. One drop of the precipitating solution given by a pipette of the above size precipitates 0·005 gramme of albumen, so that so many drops as it takes to precipitate all the albumen, so many times 0·005 gramme of albumen must have been in the solution. To save trouble in calculation, the same quantity

of urine should always be taken, and the most convenient quantity to take is 10 c.c., as then the number of drops of the solution that it takes to precipitate all the albumen in this quantity of urine represents so many half-grammes to the litre.* Take then 10 c.c. of urine, add 2 c.c. of acetic acid, and stir with a glass rod; add the precipitating solution drop by drop, stirring carefully each time, until the precipitate is no longer redissolved in the albumen in excess, *i.e.*, as yet unaffected by the reagent; after adding each drop of the solution, put a drop of the urine on a porcelain dish and watch if a yellowish-red colour appears on adding a minute drop of the confirmatory solution. As soon as it does, all the albumen is precipitated and the process is finished, and the amount of albumen per litre will be at once arrived at by taking the number of drops employed of the precipitating solution, subtracting three as having been used in excess to make the yellow colour perfectly apparent, and then considering the rest as so many half-grammes. The chemical reactions and data on which the above depends are $4KI + HgCl_2 = HgI_2, 2KI + 2KCl$. When the double iodide of mercury and potassium thus formed is added to albuminous urine sufficiently acidified, all the albumen is precipitated in combination with the mercury and iodide of the reagent in the proportion of the equivalent of HgI_2, KI ($= \frac{1}{2} HgI_2, 2KI$) weighing 393, to one equivalent of albumen $C_{86}H_{56}N_9O_{11}S$ weighing 1004, while the potassium is taken up by the acid of the urine. As long as any albumen remains in solution, the double iodide of mercury and potassium will not form red iodide of mercury when bichloride of mercury is added to it, but it does so as soon as all the albumen is precipitated. The solution formulated above is such that every drop of 0.05 gramme contains 0.00196 gramme of HgI_2, KI , and therefore, in accordance with the equivalents given, will precipitate .005 of albumen.†

Bodeker's Method.—Identical in principle with the fore-

* Supposing it takes 10 drops of the precipitating solution to precipitate the albumen in 10 c.c. of urine, then $0.005 \times 10 = .05$ gramme of albumen, and 10 drops = 10 half-grammes to the litre; for 10 : 1,000 :: .05 : 5.

† $393 : .00196 :: 1004 : 0.005$.

going process is that recommended by Bödeker. It is based upon the fact that potassic ferrocyanide completely precipitates albumen from an acid solution in the proportion of 211 ferrocyanide to 1612 albumen. The standard solution of ferrocyanide is made by dissolving 1·309 gramme of the pure salt in a litre of distilled water. One cubic centimetre of the solution thus prepared precipitates 0·01 gramme of albumen.*

Analytical Process.—Take 50 c.c. of the clear filtered urine, and mix with 50 c.c. of commercial acetic acid, and put the fluid into a burette. Five filters are then put into a corresponding number of funnels, a few drops of acetic acid being added, and filled up with boiling water. In this manner filtration takes place more rapidly. Ten c.c. of the ferrocyanide solution are then measured into a beaker with 10 c.c. of the ordinary fluid from the burette. The fluid is then shaken and poured upon No. 1 filter. If the fluid which passes through is bright and clear and of a yellowish colour, then the ferrocyanide will be in excess, and a drop of the urine added to it will produce a cloudiness. Otherwise, if not enough of the ferrocyanide has been added, the filtrate will be turbid, and pass slowly through. Frequently, in this case, both the ferrocyanide and the urine will produce a turbidity when added. The addition of too much urine in testing the filtrate for excess of ferrocyanide must be avoided, so that the precipitate of hydro-ferrocyanide of albumen may not be dissolved in the excess of albumen.

According to the result obtained from the first filter, a second trial is made, increasing the quantity of urine or ferrocyanide half, or so, as much again, and so on until it is found that the solution first shown to be in excess is reversed. The mean is now taken between this quantity and the previous one, and the final test applied.†

Example.—Fifty c.c. of urine containing albumen were mixed with a like quantity of acetic acid and tested as follows :

* $211 : 1 :: 1612 : 7\cdot6$, and $1 : 1\cdot309 :: 7\cdot6 : 0\cdot0099$.

† Sutton's 'Volumetric Analysis.'

	Urine.	Ferrocyanide.	In filtrate urine gave	In filtrate ferrocyanide gave
(1)	10 c.c.	10 c.c.	0	precip.
(2)	10 c.c.	20 c.c.	precip.	0
(3)	10 c.c.	15 c.c.	0	precip.
(4)	10 c.c.	17.5 c.c.	0	faint precip.
(5)	10 c.c.	18 c.c.	0	0

Hence 10 c.c. of the diluted urine=5 c.c. of the original secretion, contained 0.18 gramme albumen, or 36 parts per 1,000. This process is obviously more complicated and tedious than that of Tanret and Troyes, and possesses no superior advantages to commend it.

Process of Brandberg.—This process consists in an application of Heller's method, and is based on the time necessary for the appearance of the albuminous principle in certain dilutions. According to Brandberg, Heller's reaction appears as follows :

(a) Immediately, in a solution of one part of albumen in 10,000 of water (0.01 per cent.).

(b) In from quarter to half a minute, in a solution of 1 in 20,000 (0.005 per cent.).

(c) In about one minute and a half, in a solution of 1 in 25,000 (0.004 per cent.).

(d) In from two and a half to three minutes, in a solution of 1 in 30,000 (0.0033 per cent.).

(e) In about four minutes, in a solution of 1 in 35,000 (0.0028 per cent.).

Basing the following procedure on (d), the urine is diluted with nine times its volume of water (one-tenth of urine), and Heller's test is applied as follows: By means of a pipette a little nitric acid is placed in a conical glass, and similarly the diluted urine, taking care not to mix the two. If after the lapse of three minutes an albuminous ring does not appear at the point of junction of the two fluids, it may be concluded that the quantity of albumen does not exceed 0.003 per cent., and consequently in the pure urine not more than 0.03 per cent. If, on the contrary, the reaction is established within three minutes, the urine must be further diluted in the following manner: Five glasses are taken; into each glass are placed 2 c.c. of the urinary solution:

four c.c. of water are added to the first, to the second 13, to the third 28, to the fourth 43, and to the fifth 58 c.c. of water. To each of these solutions nitric acid is added with the precautions necessary in Heller's method. If one of them gives a reaction in from two and a half to three minutes, it is concluded that in that one the proportion of albumen is 1 in 30,000 or 0.0033 per cent. Knowing the number of cubic centimetres of water added, the quantity of contained albumen may be calculated by the following formula :

$$2 \times 0.1 \times x = (a + 2) \times 0.0033,*$$

in which a represents the number of c.c. of added water. The following table exhibits the proportion of albumen per cent., the number of c.c. of water added being known, and Heller's reaction being obtained in three minutes.

* Supposing, for example, 8 c.c. of water have been added, then :

$$2 \times 0.1 \times x = (8 + 2) \times 0.0033.$$

$$2 \times 0.1 \times x = (10) \times 0.0033.$$

$$2 \times 0.1 \times x = .033.$$

$$0.2x = .033, \text{ and } x = .033 \div .2 = 0.165.$$

C.C. of Diluted Urine.	C.C. of Water.	Albumen per Cent.
2+	1	=0·049
2+	4	=0·099
2+	8	=0·165
2+	10	=0·198
2+	13	=0·247
2+	16	=0·297
2+	19	=0·346
2+	22	=0·396
2+	25	=0·445
2+	28	=0·495
2+	31	=0·549
2+	34	=0·594
2+	37	=0·643
2+	40	=0·693
2+	43	=0·742
2+	46	=0·792
2+	49	=0·841
2+	52	=0·891
2+	55	=0·940
2+	58	=0·990
2+	61	=1·039
2+	64	=1·089
2+	67	=1·138
2+	70	=1·188
2+	73	=1·237
2+	88	=1·485

Hammerstein has made experiments with a view to testing the accuracy of the above, and he has shown that with a little experience the amount of variation, as tested by weighing, does not exceed 0·05 per cent.

Esbach's Process.—This method is based on the fact that picric acid precipitates albumen at the ordinary temperature, and that the precipitate deposits in a uniform state and degree of density. The apparatus employed consists of a tube, in appearance like a large-sized test-tube, but of greater thickness,

and graduated so as to indicate the amount of deposits. The graduation of the instrument represents in grammes the quantity of albumen contained in a litre of the urine operated upon, the interspaces diminishing towards the open extremity of the tube, the weight exercised by the reagent being greater on the portion of the deposit nearest it.



FIG. 33.—
ESBACH'S
ALBUMENI-
METER.

The Reagent.—Take 10 grammes of chemically pure picric acid, and 20 grammes of citric acid dried in the air. Dissolve in 800 or 900 grammes of water, and, after cooling, add sufficient water to obtain 1,000 c.c., or 1 litre.

The albuminous urine must be acid. If not acid, a few drops of acetic acid must be added. The urine is poured into the albumenimeter up to the mark U, and then the reagent is added up to the part of the tube indicated by the letter R. The fluids are then mixed without violent agitation, so as to prevent the formation of air-bubbles. This being accomplished, the open extremity is covered by means of a little gutta-percha sheeting or cork, and the instrument allowed to remain undisturbed in a vertical position for a period of twenty-four hours. At the expiry of this time, the figure indicating the height of the deposit is noted, and shows in grammes the amount of albumen contained in a litre.

The instrument is not graduated beyond 7 per 1,000. Hence, when the quantity of albumen exceeds this amount, it is necessary to dilute the urine, the result being multiplied by the amount of dilution, double or triple, as the case may be. The method is not adapted for minute quantities of albumen, as it does not indicate less than 0.1 per cent.

This process is suitable, from its simplicity, for clinical purposes; and its accuracy is such that Graaf has found that, between the results obtained with it and the polarimeter, the variation did not exceed from 0.1 to 0.2 per cent.

Zōhār's Method.—Zāhōr* has devised the following quick and ready method, which gives results accurate to the first decimal place. It depends on the difference in the specific gravity or density brought about in the urine by the removal of the albumen.

The process, which is a densimetric one, is as follows: A preliminary examination of the filtered urine is made, in order to determine approximately the amount of dilute acetic acid necessary to precipitate all the albumen when boiled. This is ascertained by placing a small quantity of urine in a test-tube with acetic acid and boiling. The coagulum is then removed by filtration. The filtrate should yield no precipitate with acetic acid and potassium ferrocyanide. A convenient quantity of the filtered urine is now placed in a flask fitted with a cork, acetic acid having been added, and the flask is then placed in boiling water for ten or fifteen minutes. This brings about the coagulation of the albumen, whereupon the fluid is carefully filtered into a flask fitted with a perforated cork, through which a funnel is passed. The density of the urine and of the filtrate is then determined by means of a urinometer, graduated to the fourth decimal place. The difference between the initial density and the final density is now multiplied by the factor 400, the product giving the number of grammes of albumen present in 100 c.c. of the urine.

Pathological Significance.—In the condition of perfect health albumen does not exist in the urine. From this standpoint, then, when it does so exist, it may be viewed as invariably possessing a pathological significance. It does not, however, follow that the appearance of albumen in the urine is necessarily due to structural change in the renal tissues, for, on the one hand, albumen may exist in the urine without any appreciable renal change, and, on the other, there may be considerable kidney change without the accompaniment of albumen in the urine. Two inferences seem to be justly deducible from these facts: on the one hand, conditions apart from the kidney may occasion albuminuria; and, on the other, it is only when special portions of the kidney are affected that albuminuria results.

* *Zeitschrift für Physiolog. Chem.* (12, 484-489).

Between the blood and the secretory apparatus of the kidney, as in the case of all the other secretory organs of the body, there is what may be called, for want of a better term, a vital correlation, whereby the cells separate from the blood the peculiar and special constituents of the urine. Why or how the cells of the various secretory organs secrete only their own peculiar secretions, to the exclusion of others, we cannot explain. We have to regard it simply as an ultimate fact. This correlation, in the case of the kidney, may be deranged from two opposite directions—viz., structural change of the kidney, unfitting it for its work as a depurating organ, or change in the blood supplied to the kidney, poisoning, so to speak, the renal tissues temporarily, or leading to permanent change. Further, given perfectly healthy blood and perfectly healthy renal structure, the blood must pass through the gland at a certain rate of circulation and a certain degree of vascular tension. Hence albuminuria may be either of a pathological or physiological nature primarily, and its varieties may be thus classified :

PATHOLOGICAL.		PHYSIOLOGICAL.	
Structural change of the kidney.	Blood changes.	Conditions affecting the circulation of blood in the kidney.	
Excess of albumen in blood.	Poisoning by phosphorus, arsenic, mercury, and lead ; pneumonia, typhus, jaundice, scarlet fever, anæmia, leucæmia, diphtheria, diabetes, hyperpyrexia ; excessive alkaliuity of the blood.	Impressions on the nerves supplying the kidney (splanchnics) ; spinal injury ; intestinal irritation ; masturbation ; cutaneous excitation (cold bathing, etc.) ; asphyxia ; cerebral exhaustion (over-study, etc.) ; menstrual disorders.	Diseases of the heart, lungs, liver, etc. ; atony of the renal bloodvessels ; increased or diminished blood-pressure ; tumours pressing on veins, pregnancy, etc.

Further consideration of these various states does not fall within the province of this work.

Therapeutical Indications.—In albuminuria arising from acute inflammation of the kidney, as in inflammatory affections of all complex organic structures, the great principle of physiological rest and vicarious action must be kept in view. Consequently the skin and bowels must be so acted upon as to spare the kidney and relieve it of as much work as possible. Hot baths and diaphoretics are therefore indicated, and such purga-

tives as remove the watery portion of the blood to the greatest extent, as elaterium, scammony, etc. Salines should on no account be administered, as they are eliminated chiefly by the kidney, and it is difficult to comprehend on what foundation in sense or reason the indiscriminate use of bitartrate of potash is advocated in acute nephritis. The same applies to large draughts of diluents, which simply increase arterial tension, induce renal embarrassment, and increased elimination of albumen. Small doses of bichloride of mercury with iodide of potassium have proved of signal benefit in my hands.

Purulent Albuminous Urine.—Urine containing pus necessarily contains albumen, so that when microscopic examination reveals leucocytes or blood-corpuscles, the presence of albumen is to be anticipated. Should the leucocytes be in such quantity as to obscure the detection of albumen by heat, the urine should be acidulated with a few drops of acetic acid, filtered, and the usual tests applied. If the quantity of albumen be very minute after the addition of the acetic acid, a saturated solution of sulphate of soda should be added. By this means albumen may be detected in the urine of men suffering from gonorrhœa, or of females suffering from acute or chronic inflammation of the genital organs.

In the case of purulent albuminous urine the question will arise, To what extent is the albumen derived from the pus alone? or is this superadded to from a renal source? The solution of these questions often rests on practical experience alone. The albumen due to pus is in relatively small proportion. In the case of a large quantity of pus with a small quantity of albumen, say 1 per cent., or a small proportion of pus with a large quantity of albumen (5 per cent., *e.g.*), the proper conclusion will be at once apparent. Confirmation must be sought in the presence in the urine of tube-casts, or renal epithelium, and in the indications afforded by clinical symptoms.

Globuline (Paraglobuline; Fibrinoplastic Substance).—The albuminous matter which exists in the blood-corpuscles has been termed *globuline* by Berzelius. It has been termed *easeine of serum* by Panum, and *paraglobuline* by Kühne. In the urine globuline is most frequently found associated with true

albumen (serine), but it may exist in an isolated condition, constituting the condition known as *globinuria*. This substance may be conveniently extracted from the crystalline lens of the ox. The other globuline contained in the blood plasma (fibrinoplastic substance) may be found occasionally in the urine, but the former is the globuline especially eliminated with the urine. Urine containing globuline presents certain characters in common with albuminous urine. It is coagulated by heat, the fluid, however, remaining milky, and the coagulum does not become dense except in the presence of a sufficient quantity of a neutral salt (chloride of sodium or sulphate of soda). Globuline is insoluble in water and alcohol and saturated solutions of neutral salts; it is soluble in acetic acid and in dilute solutions of alkaline carbonates and phosphates. In moderately concentrated solutions of neutral salts it deviates the plane of polarization to the right. In presence of mineral acids and metallic salts it gives the reactions of albumen. The point of coagulation of albumen is $72^{\circ}\text{C}.$; that of globuline is about $80^{\circ}\text{C}.$ Globuline is coagulated by alcohol, by nitric acid, by potassium ferrocyanide with acetic acid, and by Tanret's solution; so that it must be borne in mind that in albuminous urine submitted to these tests the globuline, if it exist, is also precipitated by them. The differential features of globuline as compared with albumen are as follow:

(1) Ammonia and acetic acid separately employed do not precipitate globuline, but used successively they cause a precipitate of globuline.

It is immaterial which is first added, providing the latter be added in sufficient quantity to neutralize the former.

(2) A solution of globuline is precipitated by passing a current of carbonic acid gas through it. This precipitate is redissolved by passing a current of air through the solution in like manner for a sufficient length of time.

A concentrated solution of globuline feebly acid or alkaline is precipitated by chloride of sodium. Of all albuminous substances, sulphate of magnesia *precipitates globuline alone*.

To determine for clinical purposes the presence of globuline in the urine, a saturated solution of sulphate of magnesia is employed. To the urine previously filtered an equal quantity

of the solution is added. The combined fluids are to be well shaken and allowed to rest for twenty-four hours, when, if globuline is present, it appears as a floating coagulum. In rare cases it subsides. When the urine is distinctly acid, the sulphate of magnesia solution may be added at once. When, on the other hand, it is but feebly acid or alkaline, five or six drops of acetic acid should be added for 100 c.c. The precipitate thus obtained is easily dissolved by common salt.

M. Pohl* gives preference to sulphate of ammonia over sulphate of magnesia. In testing serous liquids he adds it directly, and to acid urines after neutralization with ammonia, and separation of the phosphates by filtration. To urine thus rendered alkaline the solution of sulphate of ammonia is to be added. After an hour's repose, the precipitate is collected on a filter, washed with sulphate of ammonia, dried at 100° C., and weighed. The whole is incinerated, and the weight of the ash subtracted.

Quantitative Analysis.—In estimating the quantity of globuline in any given specimen of urine, the albumen must be previously removed, and *vice-versâ*. To determine primarily if urine contain globuline, a certain quantity of filtered urine should be diluted with fifteen or twenty times its bulk of water, and a few drops of acetic acid added, when, if globuline is present, a turbidity, or even a precipitate, results.

Process of Hammarstein.—Filter 50 c.c. (or 100 if it contain no albumen). The reaction ought to be acid. Mix with an equal quantity of a saturated solution of sulphate of magnesia, and lay aside for twenty-four hours, when flakes of globuline will have separated. The precipitate is carefully collected, the filter paper washed, first with a saturated solution of sulphate of magnesia, and then with boiling alcohol acidulated with acetic acid, and finally with boiling distilled water, which does not dissolve the globuline by reason of the addition of the alcohol and the acetic acid. Dry and weigh. The globuline may be preferentially estimated by difference. Thus—the albumen and globuline may be estimated *en masse* by coagulation. Then the

* *Archiv. für Exper. Pathol. und Rundschau für die Pharmacie*, xiii., p. 369, 1887.

globuline may be separated by sulphate of magnesia, and the fluid containing only albumen filtered. A few drops of acetic acid are then added and the albumen coagulated. From the combined weight of the albumen and globuline that of the albumen alone is subtracted, and the result is the weight of the globuline. The amount of dilution by the sulphate of magnesia solution must be taken into account.

Pathological Significance.—Globuline is almost invariably accompanied by albumen in the urine, and is usually much less abundant. In acute nephritis it becomes augmented* coincidently with the diminution of albumen, and considerable globinuria is of grave import, and a diminution of its elimination of favourable augury.

Fibrine.—When the urine contains blood, it necessarily contains fibrine. It may exist independently after acute inflammatory affections of the genito-urinary tract and kidneys, and appears under the form of a gelatinous coagulum, or a flaky mass either at the moment of emission of the urine or shortly afterwards. It sometimes exists in such abundance as to form with the urine a gelatinous mass, so that the vessel containing it can with difficulty be emptied. This form of coagulable urine is more frequently met with in warm climates, where chyluria is associated with *fibrinuria*. Hoffmann and Ultzmann have noticed a transitory fibrinuria in certain cases of villous tumours of the bladder, the urine being of a reddish or pale yellow colour. In cases of poisoning by cantharides, especially, fibrine is apt to exist in the urine.

In order to isolate this fibrine, the urine is filtered and the deposit remaining on the filter washed with water. This is insoluble in alkalies and diluted acids.

Mucine.—Mucine exists in the secretions of all the mucous surfaces of the body. Normally, it exists to a small extent in the urine—0·5 to 1·0 gramme per litre according to Meisner. Its proportion is increased when the mucous membrane of the urinary tract is irritated, as in catarrhal affections and febrile affections in general. The mucus normally found in the urine is probably secreted by itself by the glands at the level of the

* Estelle, Faveret, and Hoffmann.

trigonum vesicæ ; when the secretion is abnormally abundant, it is probably derived from the ureters and secretory structure of the kidney. Mucus existing to an abnormal extent in the urine of females is often derived from the vagina.

Mucus does not exist in the urine in a soluble form, and may therefore be separated from it by filtration.

Properties of Mucus.—Mucus is an albuminous substance of a white, flaky appearance. It absorbs, and becomes swollen by the absorption of, water. Dried by heat, it forms a gelatinous mass, on which water has little effect. It is in reality insoluble in water, in which, however, when the quantity is larger, it is capable of being so diffused as to pass through a filter as if a solution. Mucine is precipitated by acetic acid, and the precipitate is unaffected by excess of the acid. Mucine is likewise precipitated by alcohol, in which it is insoluble. It is insoluble in ether, in organic acids, and in dilute mineral acids, while it is dissolved by the concentrated. Alkalies readily dissolve mucine, notably acetate of potash. Sulphate of magnesia, bichloride of mercury, neutral acetate and sub-acetate of lead also precipitate it. It is not coagulated by heat, and on heating, acid nitrate of mercury gives with it a bright rose colour.

Analysis.—Microscopic examination does not reveal the presence of mucus, as it is so transparent as not to modify transmitted light. If acetic acid be previously added, microscopic examination reveals mucus as a delicate membrane which is coloured by tincture of iodine. Sometimes mucus appears in the form of filaments, which may be mistaken for tube-casts, and may appear opaque from a deposit on them of urate of soda. They are distinguished from casts by their size, their secondary ramifications, and their association with epithelial scales and mucous corpuscles. Acetic acid renders these filaments more apparent. Urine containing an excess of urates is precipitated by acetic acid, the precipitate being insoluble in an excess of acid, but on being heated the precipitate disappears. This distinguishes the precipitate from mucus.

When the urine is also albuminous, a few drops of acetic acid should be added, and then three or four times its volume of concentrated alcohol. After standing for some time the fluid is

filtered to separate the albumen precipitated by the alcohol, and the filtrate is mixed with an excess of acetic acid.

Leucomaines and Ptomaines.—According to Pouchet and Gautier, the urine always contains in the state of health a small proportion of *leucomaines*, or physiological alkaloids. These are considerably increased in infectious diseases, such as typhus fever, and certain nervous affections.

Robin states that in typhus fever the urine also contains *ptomaines*, or *cadaveric alkaloids*, originating in perversion of disintegration or bacterian fermentation.

PEPTONES.

Peptones are the result of the complete action of the gastric juice on albuminous substances. By *hemi-albumose* or *propeptone* is understood one of the products of this transformation. These compounds may be artificially produced by means of pepsine and pancreatine, and both are found in the urine under certain conditions, either separately or in combination with albumen.

Properties of Peptones.—Peptones are white, amorphous, and slightly bitter. They dissolve with facility in water, are crystallizable, and sparingly soluble in alcohol. They are insoluble in ether and chloroform. They are not precipitated by heat, like albumen and globuline, nor by ferrocyanide of potassium and acetic acid, like globuline, albumen and hemi-albumose; they are precipitated by tannin, a weak solution of hydrochloric acid, phosphotungstic acid, phosphomolybdic acid, metaphosphoric acid, picric acid, bichloride of mercury, nitrate of mercury, iodide of mercury and potassium (Tanret's solution), nitrate of silver, and acetate of lead in ammoniacal solution. On heating with nitric acid, like albumen, they give the coloured xanthoproteic reaction, and with caustic soda and sulphate of copper solution the characteristic red biuret reaction. With Millon's solution a red colour is produced, as in the case of albumen, but of much greater intensity.

Analysis.—The biuret reaction affords the best evidence of the presence of peptones in the urine. Should the urine contain albumen, it should be acidulated with acetic acid, and boiled

with a saturated solution of chloride of sodium. The albumen is separated by filtration and the biuret test applied to the filtrate.

Process of Hofmeister.—To the urine 2 per cent. of acetate of soda is added and perchloride of iron *guttatim* until the red colour is permanent. Neutralize the urine by an alkaline solution, and boil until all the iron is precipitated in the form of a basic acetate, carrying with it the albumen. The filtrate should be entirely free from albumen, and unaffected by the ferrocyanide of potassium test. The special peptone tests can then be applied.

Otherwise, filter about half a litre of urine, after agitation with a little neutral acetate of lead in order to eliminate and decolorize mucine if present. To a portion of the filtered fluid add from 5 to 10 per cent. of concentrated hydrochloric acid and phosphotungstate of soda, thus :

Phosphotungstate of soda	25 grammes.
Hydrochloric acid	5 „
Distilled water...	250 „

Add so long as a precipitate is formed ; filter and wash the precipitate with water containing 4 or 5 per cent. of concentrated sulphuric acid until the filtrate is colourless. Add an excess of solid hydrate of baryta, heat gently with a little water until the fluid, at first of a greenish colour, becomes yellow, filter and apply the biuret test.*

Reaction with Tanret's Solution.—Tanret's solution gives a precipitate with peptones which disappears on the application of heat and reappears on cooling. If the hot test-tube be immersed in cold water the precipitate appears at the cooled part.

Reaction with Millon's Solution.—Millon's solution gives a cherry-red colour with peptones.

Reaction with Tannin, etc.—Tannin, bichloride of mercury and chlorinated water give an abundant white precipitate with peptones.

Picric Acid Reaction.—Picric acid solution gives a precipitate with peptones which disappears on heating. Albumen may be thus separated from peptones by filtering the boiled fluid ; the

* So called because the bicianate of ammonia gives the same coloration when applied to the same principles.

peptones pass through, and leave the coagulated albumen on the filter. If the urine contain alkaloids, such as quinine, picric acid gives a similar precipitate, which dissolves on heating. If the urine contain mucine, as shown by its becoming cloudy on the addition of acetic acid, it should be separated by neutral acetate of lead.

Pathological Significance.—Peptones are found in the urine in cases of fibrinous pneumonia, acute rheumatism, phthisis, tubercular meningitis, puerperal septicæmia, and deep-seated abscesses of bone, and elsewhere, especially when a process of absorption has been established (pyogenic peptonuria of Von Jaksch); in pernicious anæmia,* progressive paralysis, and scorbutus (hæmatogenous peptonuria of Von Jaksch); in carcinoma of the stomach and in typhoid fever (enterogenous peptonuria of Maixner). Peptonuria is evidently caused by a destruction of leucocytes, or the regression of plastic exudation.

Hemi-albumose (Propeptone).—Hemi-albumose, as its name implies, is a compound intermediate between albumen and peptone. It was first described by Bence-Jones as occurring in the urine in the case of osteo-malacia. Subsequently Kühne and Salkowsky confirmed this observation. Leube found it in the urine in a case of urticaria, Neale in a case of hæmoglobinuria, and Von Jaksch in a case of tuberculosis with nephritis and peritonitis.

Properties.—Hemi-albumose gives most of the albumen reactions, but it dissolves with difficulty in cold solutions, though rapidly on boiling, by which it is contradistinguished from albumen.

Analysis.—If an excess of acetic acid be added to urine containing hemi-albumose (and neither albumen nor globuline), and *guttatim* a solution of ferrocyanide of potassium, a precipitate results, which disappears on heating. Urine rich in salts ought to be previously diluted. By saturating such urine with sea-salt, a precipitate of hemi-albumose is caused, which is increased by the addition of acetic acid, and entirely disappears on heating, reappearing on cooling.

Should the urine simultaneously contain hemi-albumose,

* *Neurol. Centralblatt* (No. 5, 1894).

albumen, and globuline, the presence of hemi-albumose is determined as follows: Saturate the urine completely with a solution of marine-salt, add an excess of acetic acid, boil and filter. The albumen and globuline remain on the filter, and the hemi-albumose passes through, and separates on cooling. The acetic acid and ferrocyanide of potassium test may also be applied to the filtrate.

Transitory Albuminuria.—The subject of transitory, or cyclical, albuminuria has of recent years received considerable professional attention, and various conflicting deductions have been drawn from the occurrence. The merit of having first directed attention to albuminuria independently of structural renal change is usually ascribed to Gubler, in 1865; but as long ago as 1852 Dr. Warburton Begbie, of Edinburgh, in a paper read before the Medico-Chirurgical Society of that city, drew attention to the subject, defining *temporary albuminuria* as 'the manifestation and continuance of albumen in the urine during a limited period, and unconnected with any serious organic change in the kidney.' The literature of the subject has been largely added to since then by many well-known observers.

The percentage in which albuminuria occurs in obviously healthy persons has been variously stated by authorities, one author (De La Celle) estimating it as high as 84 per cent.; but in this case Tanret's test seems to have been relied upon for the detection of albumen, and its fallaciousness as an albumen test has already been referred to. Dr. Grainger Stewart (*Brit. Med. Jour.*, 1887) believes that albuminuria exists in 30 per cent. of the community.

In seeking for an explanation of albuminuria, the normal function of the kidney has to be kept in view. The function of the Malpighian body is that of *filtration*; that of the cells of the convoluted tubes *excretion*—the separation of the urinary constituents from the blood. Accordingly, Bernard observed that the veins in the glomeruli contained less dark blood than the veins in general, the arterial blood not having yet parted with its vital constituents. Filtration being the function of the glomeruli, it is obvious that this function will be influenced by

the principles and conditions affecting osmosis ; hence an excess of water in the blood, and the presence of alkalies, will stimulate the act of filtration. According to Heidenhain, it is the external layer of the epithelium of the Malpighian capsule that offers resistance to the passage of albumen. If this layer be supplied with impure blood, or affected by certain poisonous substances introduced into the blood, it undergoes a change (fatty degeneration, for instance), and permits of the transudation of albumen.

The vaso-motor nerves keep the bloodvessels in a state of moderate contraction. If their ganglia are stimulated or irritated, their inhibitory power is impaired, and dilatation of the vessels ensues. Under these circumstances albuminuria (*vide* 'Anatomy and Physiology of the Kidney') is apt to occur. If the cutaneous capillaries are contracted, increased pressure takes place in the Malpighian bodies, and diuresis and albuminuria may result.

Albuminuria, in the sense that albumen in the urine is not compatible with perfect health, must always be considered as of pathological significance, though not necessarily indicating structural renal change. From these and the foregoing observations and facts the following conclusions may be drawn :

(1) That the presence of albumen in the urine of apparently healthy persons is of frequent occurrence.

(2) That position exercises an influence on the secretion of albumen, the horizontal position causing its diminution or total disappearance in the urine, it being apt to occur on rising, and especially after breakfast—a fact capable of three different explanations ; (a) The sudden dilatation of asthenic bloodvessels and interrupted circulation ; (b) the effects of digestion and gastro-intestinal irritation, and possibly an undue supply of albumen ; and (c) that the alkaline tide is highest during the morning hours (effect on osmosis).

(3) That certain diseases (*vide* p. 146) so alter the composition of the blood and its contained albumen that the vital relationship between it and the Malpighian capsule is changed, and albumen consequently transudes (*dyscrasic albuminuria*). In this case the albumen, according to Bouchard, forms a

uniformly cloudy mass, and is said to be non-retractile, in contradistinction to the flaky form of albumen (retractile), due to renal lesion, and coming directly from the blood. As a rule, the albumen in the urine arising from structural renal change is *not* precipitated by organic acids; in cyclical albuminuria, on the other hand, the proteid matter is, as a rule, precipitated by organic acids.

(4) Bodily exertion notably augments the proportion of albumen in cases of transitory albuminuria.

(5) Cold bathing causes an increase of the albumen in the urine in transitory albuminuria by increasing the vascular renal pressure.

(6) Nervous hyperexcitation of various kinds causes temporary albuminuria, such as protracted intellectual work (often in students), excessive irritation and exhaustion of the genital centres in the lumbar region, acting reflexly on the splanchnics, as from masturbation, excessive sexual indulgence, and menstruation and its disorders. Simple mental emotion may produce a similar result, as in the case mentioned by Basham of a man subject to attacks of hæmaturia, Mayer's case of hæmaturia as a sequel to a fit of passion, and the cases cited by Fürbringer of emotional albuminuria.

(7) Transitory albuminuria is more frequent among children than in adults.

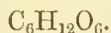
(8) Albuminous urine is usually above the specific gravity of 1014.

The quantity of albumen eliminated in various diseases ranges from 1 gramme to 20 or 30 in twenty-four hours. The albumen is said to be in *small* amount when it does not exceed 2 grammes, moderate from 6 to 8, and considerable when exceeding from 10 to 12 grammes.

Pathological Significance.—As to prognosis, the absence of tube-casts and a high specific gravity justify a favourable prognosis. It is the retention of urinary products, and not the loss of albumen to the blood, that causes death in albuminuria. Cases have been known in which albuminuria existed for over thirty years. In all such cases the specific gravity of the urine continues high.

GLUCOSE (DIABETIC SUGAR).

History—Chemistry of Sugars—Tests for Sugar in the Urine—Trommer's Reaction—Fallacies of Trommer's Test—Fehling's Reaction—Fallacies of Fehling's Test—Purdy's Method of Estimating Sugar in the Urine—Schmiedeberg's Solution—Crismer's Test—Bismuth Reaction of Böttiger—Hoppe-Seyler's Reaction—Almen's Reaction—Indigo Reaction—Phenyl-Hydrazine Reaction—Agnosti's Reaction—Picric Acid Reaction—Fermentation Test—Specific Gravity of Diabetic Urine—Quantitative Analysis—Urine containing less than 5 per cent. Sugar.—Duhomme's Quantitative Analysis—Approximate Estimate of Sugar by Specific Gravity—Gerrard's Percentage Glycosometer—Optical Quantitative Analysis—Pathological Significance — Idiopathic Glycosuria — Therapeutic Indications—Simulated Glycosuria.



Carbon	40.00
Hydrogen	6.66
Oxygen	53.34
				100.00

According to the writings of Celsus, Aretæus and Galen, the disease termed 'diabetes' (*διά*, 'through,' *βαίνο*, 'I go') seems to have been recognised in a general way by the ancients. The progressive emaciation characteristic of the malady was observed as being accompanied by inordinate thirst, voracious appetite, and excessive discharge of urine. It was not, however, until 1674 that the urine in certain cases was discovered to possess a sweet taste, and the honour of this discovery, on which followed the establishing of the distinction between *diabetes insipidus* and *glycosuric diabetes*, is due to Willis, an English physician. A hundred years subsequently, Dobson, of Liverpool, discovered that the blood as well as the urine contained sugar; and he inferred therefrom that this sugar was separated from the blood, and not formed by the kidney. In 1778 Cowley separated the sugar from the urine in a free state. In 1815 Chevreul pointed out that the sugar existing in the urine in cases of *diabetes mellitus* was different from cane sugar and closely resembled that of the grape; and in 1825 Tiedmann and Gmelin ascertained that during its passage along the alimentary canal starchy matter was transformed into sugar.

Normally, sugar is found in the small intestine, and in the chyle after the ingestion of saccharine or starchy matter, and in the blood. The hepatic vein (Claude Bernard) abounds in it, while it does not exist in the portal, a fact demonstrating the sugar-forming function of the liver. This sugar is formed from an intermediate albuminoid product called glycogen, belonging to the amyloid group. This is a white substance which iodine colours violet-blue, and nitric acid transforms into xyloidine, an explosive material like gun-cotton. Sugar is not burned off in the liver, but disappears in the capillary system, after undergoing a series of changes, ultimately represented by water and carbonic acid. Temporary glycosuria may be occasioned, according to Frerichs, by (a) poisoning by carbonic oxide, curara, nitrate of amyl, and large doses of morphia, chloral, prussic acid, sulphuric acid and alcohol; (b) by digestive derangements, catarrh of the stomach, cirrhosis of the liver, thrombosis of the portal vein; (c) by derangements of the nervous system, neuralgia, sciatica, lesions of the spinal cord, cerebral excitement, disseminated sclerosis, apoplexy, etc. According to Worm-Muller cane-sugar, grape-sugar and milk-sugar, taken in doses of from 50 to 250 grammes, pass directly into the urine, causing temporary glycosuria. Levulose, taken even in large doses, is never found as such in the urine.

Milk-sugar sometimes appears in the urine after child-birth, and especially when the secretion of milk by the mammæ is embarrassed. Hofmeister and Kaltenbach have also found it in the urine of infants exclusively fed upon milk.

Bernard has caused the appearance of sugar in the urine by pricking the floor of the fourth ventricle. It is sometimes alleged that sugar exists normally in urine in very small quantity, but this has not been satisfactorily demonstrated.

Chemistry.—Sugars are divided into the following groups:

(Glucoses) $C_6H_{12}O_6$	{ Glucose, or Dextrose, or Grape-Sugar. Levulose.
(Saccharoses) $C_{12}H_{22}O_{11}$	{ Cane-Sugar or Sucrose, Maltose. Lactose or Milk-Sugar.
(Amyloses or Amyloids) $C_6H_{10}O_5$	{ Dextrine. Starch. Cellulose.

Glucose (sugar of diabetes), in its perfectly pure state, is of white appearance. It most frequently presents a yellowish colour. Its crystalline character is quite different from that of cane-sugar. It crystallizes in four or six sided rhomboidal prisms, while grape-sugar occurs in small cubes or square plates.

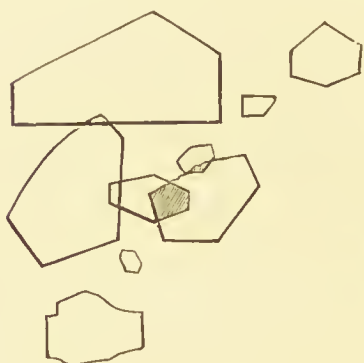


FIG. 34.—TABULAR CRYSTALS OF GRAPE-SUGAR.

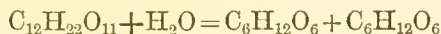
It is less sweet than cane sugar, and less soluble in water, but more soluble in alcohol. It is insoluble in ether. Sucrose and glucose possess right-handed rotation, and deviate the ray of polarized light from left to right according to the amount of sugar present, a fact by which its amount in diabetic urine may be estimated.

Glucose combines readily with caustic alkalies, forming glucosates. Thus it combines with lime, baryta and potash. If an alcoholic solution of potash and glucose be mixed, glucosate of potash immediately precipitates in white flakes. If the mixture be subjected to heat, it becomes of a yellow or dark-brown colour, owing to the formation of glucic and melassic acid, according to the quantity of glucose and potash present (Moore-Heller's Reaction).

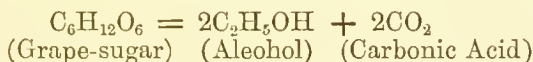
If to a soluble glucose an excess of potash or soda be added, and a solution of sulphate of copper, the result is a bluish alkaline liquor, which, on being heated, gives a yellowish-red precipitate of protoxide of copper (Cu_2O) (reaction of Trommer, Fehling and Worm-Muller).

Glucose is acted on by mineral acids, by which it is transformed into black or brownish products. Nitric acid oxidizes it, forming oxalic ($\text{H}_2\text{C}_2\text{O}_4$, $2\text{H}_2\text{O}$) and saccharic acid ($\text{H}_2\text{C}_6\text{H}_8\text{O}_8$). Acted upon by hydrochloric or sulphuric acid, cane-sugar is converted into grape-sugar. This is easily demonstrated in the following manner: Dissolve a few grains of cane-sugar in water in a test-tube. Add a few drops of a solution of sulphate of copper and a considerable quantity of a solution of potash, and heat the

mixture to the boiling-point. No change occurs. To another portion of the sugar solution add a drop of sulphuric acid, and boil for ten or twenty minutes. Add the solution of sulphate of copper and potash as above, boil, and a yellowish-red precipitate of cuprous oxide (Cu_2O) immediately falls. Here the acid has converted the cane-sugar ($\text{C}_{12}\text{H}_{22}\text{O}_{11}$) into 'invert sugar' (a mixture of dextrose and levulose), so-called because it rotates a ray of polarized light to the left, whereas cane-sugar is dextro-rotatory.



Both cane-sugar, maltose and grape-sugar yield alcohol and carbonic acid by fermentation. The cane-sugar probably always passes into grape-sugar before the production of alcohol begins.



Extraction of Glucose from Diabetic Urine.—Evaporate the urine on a water-bath until it is of a syrupy consistence; leave it to settle in a cold place, when, at the expiry of a few days, a crystalline deposit will have formed. By treating these crystals with absolute alcohol, urea and extractive matter are separated. They are then dissolved in boiling alcohol and the solution evaporated.

TESTS FOR SUGAR IN THE URINE.

Moore's Reaction.—Equal quantities of non-albuminous urine and a solution of caustic potash are to be mixed in a test-tube. The earthy phosphates are first precipitated, and may be separated by filtration. The fluid is then boiled, when, if it contain sugar, it assumes a colour passing from pale yellow to dark brown. The colour is due to the successive formation of glucic and melassic acids, and disappears on the addition of a few drops of nitric acid, the characteristic odour of caramel being evolved. For the purpose of comparison, it is better to confine the action of heat to the upper portion of the tube. Unless the urine contain a considerable quantity of sugar (3 per cent., or $1\frac{1}{2}$ grains to the ounce), the test is not sufficiently discriminating.

Bouchardat prefers lime to the potash solution, as the latter colours many of the extractive matters of the urine.

Fallacies of Moore's Test.—Urine containing the pigments of rhubarb and senna becomes reddish-brown on the addition of alkalis when cold. Urine containing pyrocatechin becomes brown on exposure to air, especially after the addition of an alkali.

Trommer's Reaction.—This test is based on the property which grape-sugar possesses of reducing oxide of copper in alkaline solutions by the aid of heat. To about 5 c.c. of filtered urine free from albumen (it is not necessary to remove the albumen if it does not exceed 0·2 per cent.), add from 1 to 2 c.c. of a 10 per cent. solution of potash or soda. A 10 per cent. solution of sulphate of copper is added drop by drop until the bluish precipitate of hydroxide of copper ceases to dissolve. If the urine contain sugar, a considerable quantity of the oxide of copper is dissolved, and the liquor assumes an azure blue appearance. Heat is applied to the boiling-point, when, towards the upper portion of the tube, a yellowish-red precipitate of protoxide of copper appears. The heat is then withdrawn, and the reaction continues to extend throughout the liquid. This reaction is sufficiently marked when the proportion of sugar is not under 0·2 to 0·3 per cent.

Fallacies of Trommer's Test.—Trommer's test is not reliable when the quantity of grape-sugar is small. Uric acid, creatinine, and certain extractive matters, reduce the copper solution when the sugar is absent, and especially if the urine be concentrated. The reduction by these substances, generally speaking, takes place only at the boiling-point. Exception, however, is to be noted in the case of uric acid, a precipitate of oxide of copper often forming at 90° or 100° Fah. In consequence of this source of fallacy, too strong heat should not be employed, nor should its action be long continued. In some cases, secondary reduction of the copper takes place. This does not indicate the presence of sugar, as the action in this case is immediate. Trommer's test has thus to be performed with care. In doubtful cases, only a few drops of the solution of copper (1 to 3) should be added. If, on the application of heat, reduction is manifested

by decoloration, more solution has to be added, until a decided reaction is produced.

Fehling's Reaction.—This test is also based on the reduction of an alkaline solution of copper by glucose. The solution is prepared as follows: 34·65 grammes of pure dry crystals of ordinary sulphate of copper are dissolved in about 250 c.c. of distilled water; 173 grammes of pure crystals of double tartrate of potash and soda (*sel de Seignette*) are dissolved in 480 c.c. of a solution of caustic soda of sp. gr. 1·14. The solutions are mixed, and water added to 1 litre. A clear, deep blue solution is thus obtained, Fehling's solution, of which 100 c.c. represent 3·464 grammes of sulphate of copper, and correspond to 0·5 of a gramme of pure anhydrous grape-sugar, 0·475 of cane-sugar, 0·82 of maltose, and 0·45 of starch.

Place 5 or 6 c.c. of Fehling's solution in a test-tube, and boil. If there is no precipitate, which shows that the reagent is pure, the suspected urine is added by pouring it carefully along the tube, so as to be superimposed on the test solution. If sugar be present, on boiling a greenish layer first appears, rapidly passing, through yellow, to orange or red, the precipitate extending to the entire fluid. If the sugar be in small quantity, the fluid must be boiled for a few minutes. This method is preferable to adding the reagent to the boiling urine.

*Modification of Fehling's Solution, by Ost.**—The solution recommended by M. Ost contains per litre, crystallized sulphate of copper 23·5 grammes, dry carbonate of potash 250 grammes, bicarbonate of potash 100 grammes. This solution offers the following advantages over Fehling's solution: It can be kept without undergoing change, and it less profoundly decomposes the sugars during determination. 50 c.c. of this solution correspond to 100 milligrammes of inverted sugar, 102·5 milligrammes of dextrose, 90 milligrammes of levulose, and 117 milligrammes of galactose.

Fallacies of Fehling's Test.—If Fehling's solution be too long kept, it spontaneously undergoes a process of reduction. This is said to be due to the formation of racemic or paratartaric acid, into which exposure converts the tartaric acid. If no precipitate

* *Zeitschrift für Anal. Chemie*, xxxix. (1891).

occur with Fehling's solution on boiling, its delicacy is unimpaired; but if so, a little more potash or soda should be added, and the liquid filtered, when it is again available. It is sometimes recommended to keep the copper and the alkaline solutions separately, and mix only when required for use; but this is quite unnecessary if the foregoing precautions be observed.

The addition of glycerine to Fehling's solution has been recommended for longer preservation, but it must be remembered that the glycerine of commerce is almost invariably impure.

In employing Fehling's solution, any albumen contained in the urine must be separated by coagulation by heat, or precipitation by subacetate of lead. If the urine contain albumen, the reduction is prevented, and the fluid becomes of a violet colour. The presence of ammoniacal salts also interferes with the reduction, a part of the soda of the 'Fehling' being used up by the salts. Should the urine have undergone ammoniacal fermentation, it should be boiled with a solution of caustic soda so long as ammonia is given off. It may subsequently be tested for sugar. Uric acid and urates also cause a reduction of the copper, especially after protracted boiling and during the process of cooling. This source of error may be evaded by treating the urine with subacetate of lead, which removes albumen and urates. Any quantity of sugar exceeding 3 to 4 per 1000 is readily detected by Fehling's solution ordinarily employed.

It sometimes happens that glucose in diabetic urine is replaced by dextrine. In this event, according to Bouehardat, the copper reduction takes place only after prolonged boiling.

The urine of individuals taking turpentine, copaiba, chloroform, chloral, camphor and cubebs, reduces the copper solution. Pyrocatechin, benzoate of soda, and glycerine, also reduce 'Fehling.'

The precipitate of the phosphates caused by the mixing of the two fluids sometimes persists in a state of fine division, and may be mistaken for copper reduction. The colour of the precipitate is, however, different, and after a few minutes' repose the phosphates settle in the bottom of the tube, while the copper suboxide remains suspended for many hours.

Purdy's Method of Estimation of Sugar in the Urine.—Instead of Fehling's solution, this author employs the following:

Pure sulphate of copper	4.15	gm.
Pure mannite	10	"
Caustic potash	20.40	"
Ammonia (D=0.880)	30	"
Glycerine	50	c.c.
Distilled water q.s. to	1000	"

The sulphate of copper is first dissolved in water, and the glycerine and mannite are then added; the potash is separately dissolved in water, and after cooling the two solutions are mixed. The ammonia is added, the solution is carefully filtered, and distilled water is added to make the solution up to a litre. 25 c.c. of this solution are reduced by 15 milligrammes of glucose; the deep blue coloration disappears, and the result is a perfectly clear, colourless liquid. The copper solution should be heated in a capsule to the boiling-point, and the urine added drop by drop at intervals of from two to three seconds. The results are very accurate. If the sugar is in great quantity, the urine should be diluted with water (*Pharm. Zeitsch. für Russ.*, xix., 1890).

Schmiedeberg's Solution.*—In Schmiedeberg's formula, mannite replaces the potassio-tartrate of soda. The solution is prepared as follows: Dissolve 34.632 parts of crystallized sulphate of copper in 200 c.c. of water, and 15 grammes of pure mannite in 100 c.c. of water. These two solutions are combined, and 480 c.c. of a solution of caustic soda, sp. gr. 1.145, added, and sufficient water to make 1000 c.c. According to Schmiedeberg, this solution keeps better than Fehling's.

Crismer's Test.—M. Crismer has recently advocated the use of safranin as a test for sugar. If 1 c.c. of saccharine urine be heated to ebullition with 5 c.c. of a solution of safranin and 2 c.c. of caustic potash solution, discoloration of the safranin at once takes place. On cooling, the solution becomes turbid. This reaction has the advantage over Fehling's solution in not being decolorized by uric acid, creatinine, chloral, chloroform, peroxide of hydrogen, nor the hydroxylamine salts. Albumen decolorizes it but slowly.

Bismuth Reaction of Böttiger.—If a solution of glucose with a concentrated solution of caustic soda or carbonate and

* *Journal de Pharmacie de l'Alsace-Lorraine*, January, 1886.

a little nitrate of bismuth be heated together to the boiling-point, metallic bismuth* is obtained as a fine black powder. This reaction demonstrates the presence of 0·1 per cent. of sugar. Nitrate of bismuth is neither reduced by uric acid nor creatinine, but it is reduced on prolonged heating by other indeterminate substances. In albuminous urines a sulphide of bismuth may be produced by this test. Albumen should, therefore, be previously separated.

Hoppe-Seyler's Reaction.†—The following reagent is recommended by Hoppe-Seyler. The reaction is based on the formation of O-nitrophenyl-propionic acid from indigo, when the latter is boiled with an alkali and a reducing substance. The process is as follows: Take 5 c.c. of a half per cent. solution of O-nitrophenyl-propionic acid in soda and water, and boil during thirty seconds with ten drops of the urine to be examined. If the mixture becomes of a deep blue, it contains a reducing substance equal to at least 0·5 per cent. of sugar. Normal urine thus treated becomes of a green colour. The presence of albumen in urine does not prevent this reaction, and the minutest quantity of sugar is thus detected.

Almen's Reaction.—This reagent is made according to the following formula: 10 grammes of nitrate of bismuth, 40 grammes of crystallized nitrate of potash and soda, 62 grammes of caustic potash and distilled water to 500 c.c. About 5 c.c. of the urine are mixed with from 0·5 to 1 c.c. of Almen's liquor, and heated to boiling for one or two minutes. If the urine contain a moderate amount of sugar, it becomes of a dark colour, which deepens with the continuance of heat until it becomes brownish black. This test demonstrates the existence of from 0·1 to 0·05 per cent. of sugar.‡ After the ingestion of turpentine and rhubarb, it gives with the urine a similar black colour, in the latter case due doubtless to its action on chrysophanic acid.

Indigo Reaction.—In order to apply this test, any albumen

* Probably mixed with Bismuth oxide.

† 'Ueber eine Reaktion zum Nachweis von Zucker im Urin, Auf Indigobildung,' *Zeitschrift f. Physiolog. Chemie*, 1892, t. xvii., p. 83.

‡ *Annal. de la Société Med. Chir. de Liège, et Répertoire de Pharmacie*, March, 1889.

which the urine may contain must be removed by precipitation and filtering. It must then be rendered alkaline by a solution of bicarbonate of soda. A solution of indigo is then added to the extent of causing a well-marked blue colour. On being heated, the liquor, if it contains sugar, becomes almost completely decolorized, passing through violet, purple-red, red, yellow to pale yellow, and on exposure to the air it resumes its original colour, passing inversely through the foregoing shades of colour (Mülder's reaction).

Phenyl-Hydrazine Reaction.—This test is as follows: A small portion of hydrochlorate of phenyl-hydrazine with twice the quantity of sodium acetate is placed in a test-tube half filled with water, and warmed. After adding an equal volume of the solution to be tested, the mixture is boiled for twenty minutes, when, on cooling (sugar being present), yellow crystalline needles of a compound of glucose and phenyl-hydrazine (phenyl-glucosazine) are deposited. These crystals have a definite melting-point of 204° to 205° C. This is a very delicate test, and is applicable to the detection of very small quantities of sugar. In normal urine, in the hands of Von Jaksch, a negative result was always obtained with this reagent.

Agnosti's Reaction.—To detect glucose in aqueous solutions Agnosti recommends the following: Five drops of chloride of gold (1 per 1,000) and two drops of a 5 per cent. solution of caustic potash are added to the suspected fluid. It is then boiled, when, on cooling, if it contain glucose, it assumes a violet colour if the solution be aqueous, and a port-wine colour if of urine. The other elements of the urine do not give this reaction. If albumen be present, it should be previously removed.

Picric Acid Reaction.—A solution of potash and a few drops of picric acid solution added to saccharine urine cause a deep-red coloration, due to the formation of picraminic acid.

Fermentation Test.—To apply this test two flasks are taken (Fig. 35): Into the flask A from 20 to 30 centimetres of urine are introduced, with a little yeast and a pinch of tartaric acid. The neck of the flask is closed with a cork pierced by two tubes, the tube *a* passing to the bottom of the flask, and a second tube (*c*) connecting with B, and passing to an equal depth. The flask B

is half filled with a solution of lime or baryta, and the orifice (*b*) of the tube *a* is sealed with a piece of wax. The apparatus is placed in an atmosphere with a temperature of 15° to 20° C. (59° to 77° Fahr.). Within twelve hours fermentation will take place, as evinced by the evolution of carbonic acid gas from the flask A, and the formation of a precipitate of carbonate of lime or baryta in the flask B. To be certain that the carbonic acid does not proceed from the decomposition of the yeast alone, the experiment should be repeated, employing pure water instead of the fluid supposed to contain sugar. Theoretically, 48·89 parts of carbonic acid correspond to 100 of glucose; but according to

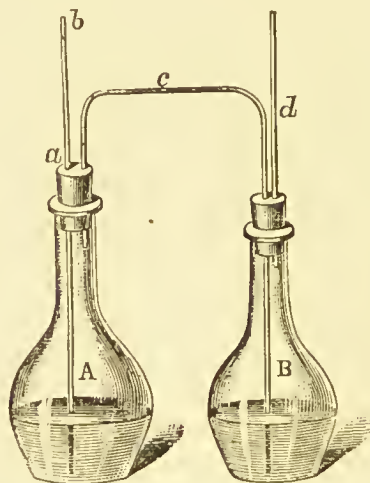


FIG. 35.—FERMENTATION APPARATUS.

Pasteur, not only are alcohol and carbonic acid formed in the process of alcoholic fermentation, but likewise a little glycerine and succinic acid. Hence in practice it is found that 48·88 correspond to 100 parts of glucose. Sir William Roberts has shown that after fermentation 'the number of degrees of "density lost" indicated as many grains of sugar per fluid ounce.'

Specific Gravity of Diabetic Urine.—While a high specific gravity does not absolutely demonstrate the presence of sugar in urine, when it exceeds 1036, in pale urine, the chances are largely in favour of the presence of sugar.

Quantitative Analysis.—The amount of sugar contained in any solution may be determined chemically or optically. In the former method, which is absolutely accurate, Fehling's solution is conveniently employed as a standard reagent. One c.c. of this solution is reduced by 0.005 of glucose (10 c.c. are consequently equal to 0.05). Into a porcelain capsule pour 10 c.c. of Fehling's solution, which dilute with 40 c.c. of water. Into a burette, graduated to tenths of a c.c., put, for example, 10 c.c. of urine, diluted with, say, five times its volume of water. The Fehling's solution is now completely boiled over a spirit-lamp; and the diluted urine from the burette carefully mixed with it, until the decoloration is complete, and a red precipitate of oxide of copper, or a yellow one of the hydrated oxide, appears. On referring to the burette, suppose you find, for example, that 9 c.c. of the diluted urine have been used to effect this change, then 1.5 c.c. of pure urine reduces 10 c.c. of Fehling's solution; and as 10 c.c. of Fehling correspond to 0.05 grammes of glucose, 1.5 c.c. of this urine must contain 0.05 grammes of glucose, = 33.33 gms. per litre (1.5 : 1000 :: 0.05 : 33.33). In order to obtain exact results in this experiment, the urine must be previously filtered, any albumen separated, and it ought to be so diluted as to contain not more than 5 per cent. of sugar, It is important to note when the blue colour has completely disappeared, and complete reduction of the copper has taken place. To determine this, the fluid is to be rapidly filtered, and one portion of it boiled with Fehling's solution, and another with diluted urine. No precipitate should result in either case. If in the first instance a precipitate forms, it is obvious that too much urine has been added, and in the second, not sufficient. The experiment should be repeated, and the mean of successive trials taken in order to obtain conclusive results. Or if to about 1 c.c. of the filtered fluid a few drops of a solution of ferrocyanide of potassium be added, and a brown colour results, it is shown that non-reduced copper still exists.

Urine containing less than 5 per Cent. of Sugar.—While, on the one hand, if the urine be rich in glucose, it is better to dilute the solution so as to contain about 10 grammes per litre, on the other, if the proportion is below 5 per cent., the influence

of other substances, which interfere with the copper reduction, is more appreciable; hence it is necessary to purify the urine by treating it with basic acetate of lead in the following manner: To 10 c.c. of urine in a graduated burette, add a tenth of its volume of subacetate of lead; shake well, and filter. To remove the lead, a weak solution of carbonate of soda should be added to make the volume equal to 50 c.c.; mix well, filter, and apply the Fehling test.

Table indicating the Amount of Sugar per Litre in Urine estimated by Fehling's Solution.

Quantity of Fehling's Solution.	C.C. of Urine necessary to decolorize.	Amount of Glucose per Litre.	Quantity of Fehling's Solution.	C.C. of Urine necessary to decolorize.	Amount of Glucose per Litre.
		Gr.			Gr.
10 c.c. of Fehling's Solution.	1.0	50	10 c.c. of Fehling's Solution.	12.5	4.00
	1.5	33.33		13.0	3.84
	2.0	25		14.0	3.75
	2.5	20		15.0	3.33
	3.0	16.66		16.0	3.12
	3.5	14.275		17.0	2.94
	4.0	12.50		18.0	2.77
	4.5	11.11		19.0	2.63
	5.0	10		20.0	2.50
	5.5	9.09		21.0	2.38
	6.0	8.33		22.0	2.27
	6.5	7.69		23.0	2.17
	7.0	7.11		24.0	2.08
	7.5	6.66		25.0	2.00
	8.0	6.25		30.0	1.665
	8.5	5.88		35.0	1.428
	9.0	5.55		40.0	1.25
	9.5	5.25		45.0	1.11
	10.0	5		50.0	1.00
	10.5	4.76		60.0	0.83
	11.0	4.54		70.0	0.71
	11.5	4.34		80.0	0.63
	12	4.15		90.0	0.55
				100.0	0.50

Duhomme's Quantitative Analysis.—In this process the chemical principles are the same as in that by Fehling's solution,

but the apparatus and subsequent calculations are different, and both are exceedingly simple. This method is, therefore, admirably adapted for clinical purposes. The apparatus required consist of some ordinary test-tubes, and two of Limousin's pipettes graduated to 1 and 2 c.c. respectively. Like all other fluids of the economy, the urine varies in composition and specific gravity from time to time. With these varying conditions, the number of drops contained in a given amount of urine—say, 1 c.c.—will correspondingly vary. A pipette is filled to the extent of 2 c.c. with Fehling's solution, which are transferred to a test-tube, and diluted with an equal quantity of liquor sodæ, or water, which does equally well. A centimetre of urine is drawn into another pipette, and the number of drops which it contains is estimated, in the first instance, by allowing the fluid to escape *guttatim* from the pipette, by exercising gentle pressure on its indiarubber cap. No further measurement is required for that urine, as with the same pipette the number of drops will always be the same. The number of drops in 1 c.c. being ascertained—say, *e.g.*, 24 drops—the urine pipette is again filled, and the 2 c.c. of 'Fehling' are boiled, and its decoloration produced drop by drop by the saccharine urine. If 8 drops, *e.g.*, are found to have decolorized the 2 c.c. of 'Fehling,' then this amounts to $\frac{8}{24}$ of a c.c., and 2 c.c. of 'Fehling' correspond to 1 centigramme of glucose. Rule: Multiply the number of drops contained in 1 c.c. of urine by 10, and divide the product by the number of drops required to decolorize 2 c.c. of 'Fehling,' and the quotient will represent the number of grammes and centigrammes of sugar per litre ($8 : 24 :: 1 : 3$, and $3 \times 1000 = 3000 \div 100 = 30$ grammes; *i.e.*, if 1 c.c. of urine contain 3 centigrammes, a litre must contain 30 grammes).

Approximate Estimate of Sugar by Specific Gravity.—

According to Bouehardat, the amount of sugar in urine may be approximately determined as follows: The density of the urine being determined by the urinometer, the two final figures above 1000 are multiplied by 2, and the number thus obtained, by the number of litres of urine voided in twenty-four hours. From this deduct 60, which represents the average quantity of solid matter other than sugar, and the remainder will represent the

amount of sugar in the volume of twenty-four hours' urine. Supposing 4 litres of urine have been passed in twenty-four hours of a specific gravity of 1036, then $36 \times 2 \times 4 = 288$ grammes, which represents the total solids in twenty-four hours' urine; then $288 - 60 = 228$ grammes of sugar, or 57 grammes per litre. Allowance has to be made for temperature.

Gerrard's Percentage Glycosometer. — This instrument consists of a burette graduated to read the percentage of sugar, or grains per ounce, in urine, without the need of any calculation.

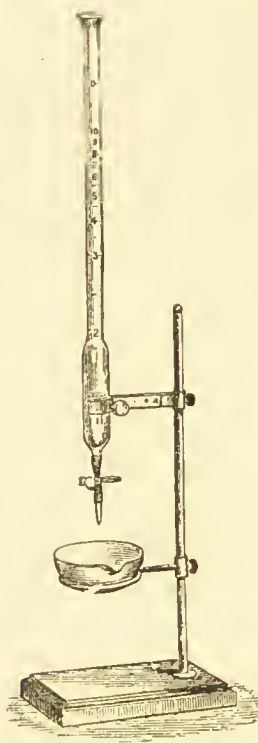


FIG. 36.—GERRARD'S
PERCENTAGE GLY-
COSOMETER.

Analysis.—Take either 10 drachms or 10 c.c. of urine which is found to contain sugar, and dilute with water to 100 drachms or 100 c.c. Mix well. Then introduce 10 c.c. or $2\frac{1}{2}$ drachms of Fehling's solution, and 40 c.c. (10 drachms) of water into the porcelain dish and boil. While the reagent is boiling, run the urine from the burette into the dish in a slow stream until the blue colour of the 'Fehling' has disappeared. The level of the urine in the burette shows the percentage of sugar present, and the equivalent in grains is given in the annexed table. As the instrument is graduated to read percentages between 10 and 1 should the urine contain more than 10 per cent. of sugar, dilute 10 volumes to 200 with water, proceed as before, and multiply the percentage by 2. If the percentage be less than 1, undiluted urine is to be used, and the reading divided by 10.

Table showing the Percentage equivalent in Grains per Fluid Ounce.

Percentage.	Grains per Fluid Ounce.	Percentage.	Grains per Fluid Ounce.
10.0 ...	43.75	1.9 ...	8.3
9.5 ...	41.55	1.8 ...	7.9
9.0 ...	39.4	1.7 ...	7.45
8.5 ...	37.2	1.6 ...	7.0
8.0 ...	35.0	1.5 ...	6.55
7.5 ...	32.8	1.4 ...	6.1
7.0 ...	30.6	1.3 ...	5.7
6.5 ...	28.45	1.2 ...	5.25
6.0 ...	26.25	1.1 ...	4.8
5.5 ...	24.05	1.0 ...	4.4
5.0 ...	21.9	.9 ...	3.95
4.5 ...	19.7	.8 ...	3.5
4.0 ...	17.5	.7 ...	3.05
3.5 ...	15.3	.6 ...	2.6
3.0 ...	13.1	.5 ...	2.2
2.5 ...	10.95	.4 ...	1.75
2.0 ...	8.75		

Optical Quantitative Analysis.—This process is based on the property which sugar possesses of deviating the plane of polarization to the right. For aqueous solutions of sugar it is well adapted, but not for urine. As the result of numerous analyses by Worm-Müller, he found that when urine contained more than 5 per cent. of sugar the polariscope gave lower figures. This depends, according to Kutz, on the fact that in grave forms of diabetes the urine contains oxybutyric acid, which is levogyrate and non-fermentable; and, according to Seegen, the urine may contain *levulose*. This process is therefore more suited to the chemical laboratory than for the purposes of the clinician.

Pathological Significance.—Sugar exists normally in the blood of man, in all the mammalia, and in almost all the animal series. In the condition of perfect health it disappears in the tissues by undergoing a process of oxidation, being thus converted into water and carbonic acid. The presence of a small quantity of glucose in the urine is held by some authorities

to be quite compatible with perfect health (physiological glycosuria), but the proportion, according to Worm-Müller, does not exceed from 0·025 to 0·5 per cent.

According to Bouchard,* glycosuria appears when the blood contains more than from 4 to 6 grammes of sugar per kilogramme. Temporary or physiological glycosuria may be occasioned by the ingestion of large quantities of sugar, or of substances such as milk, starch, etc., capable of being transformed into sugar in the process of digestion (alimentary glycosuria). Of this nature is likewise the glycosuria observed in females after child-birth, in females nursing, and in certain pregnant females. The physiological sympathy between the uterus and mammæ is disturbed; and notably, when the secretion of milk is arrested, glycosuria appears; while, conversely, if the secretion of milk be abundant, it is rarely found.

Glycosuria may be a symptom of transient impressions on the system (symptomatic and toxic glycosuria), and is thus found in cases of poisoning by phosphorus, arsenic, carbonic oxide, curara, turpentine, nitrate of amyl, morphia (in large doses), chloral, chloroform, alcohol, hydrocyanic acid, mercury, etc. It is also found co-existent with such independent diseases as pneumonia, phthisis, yellow atrophy of the liver, thrombosis of the portal vein, chronic gastritis, malaria, cerebral tumours, and hæmorrhage, lesions of the brain and spinal column, psychical hyperexcitation, etc. These several conditions resolve themselves finally into impressions on the nervous system, some ill-defined aberrant condition being the primary factor in their causation.

Idiopathic Glycosuria.—The most prominent feature of this condition is polyuria, with progressive emaciation. While emaciation is the rule, exceptional cases are sometimes encountered in which the patient does not lose much flesh, when, indeed, a certain amount of *embonpoint* exists. In these cases it is found that the amount of urea in the urine is diminished, while in the former it is much increased. In such cases Garrod has found as much as 70 grammes of urea in the daily excretion of urine, with 226·46 grammes of sugar.

* *Maladies par Relentissement de la Nutrition*, 2nd edition, Paris, 1885.

Diabetic urine, in addition to being abundant, is usually of a pale straw-colour, of a saccharine odour, often compared to the smell of violets, musk, etc., and of a high specific gravity, as a rule ranging from 1025 to 1050. When the quantity of sugar is less abundant, the specific gravity may descend to 1010. Uric acid and earthy phosphates are sometimes found in saccharine urine. After the lapse of from two to three days such urine undergoes fermentation, and is found to contain the *Penicillium glaucum*, and spores analogous to the ferment of beer, which decompose the sugar into alcohol and carbonic acid. On the drying of clothes which may have been saturated with saccharine urine, a white powdery deposit is left, which is often the first thing to attract the attention of the patient.

The amount of glucose contained in the daily discharge of urine varies from 80 to 100 grammes on an average. Jaccoud places it as high as 500 grammes, while in exceptional cases it reaches the high figure of 1,200 to 1,375 grammes (Lécorche, Féréol). The proportion of glucose is found to vary in the same individual according to the time at which it is excreted; thus, the urine of the day contains more (muscular exertion no doubt contributing to this) than that of the night. In advanced diabetes the reverse is the case. Glucose reaches its maximum in the urine after food, and especially so if starchy constituents have been partaken of. In order to estimate, therefore, the amount of glucose, a specimen of urine should be taken from the combined amount passed in twenty-four hours.

Nitrogenous diet and abstinence diminish the amount of glucose in the urine, and cane-sugar and starch augment it. Glycerine, saccharine, lactose, and levulose seem to exert no influence over it.

Diabetic urine sometimes contains albumen, and this is doubtless due to the transitory irritation and hyperæmia, as in the case of bile and other substances, which cause even the formation of tube-casts. Levulose and inosite often co-exist with glucose in diabetic urine, and occasionally dextrine almost entirely replaces glucose.

Oxybutyric acid, acetone, and alcohol may also be found in diabetic urine. Oxybutyric acid deviates the plane of polarization

to the left, and the error which may thus arise should be corrected by the use of Fehling's solution. Chloride of sodium is often diminished in quantity in diabetic urine.

Phosphaturia, oxaluria, and azoturia may co-exist with, and sometimes take the place of, glycosuria.

Therapeutic Indications.—Glycosuria appears to be due to some obscure disease of the nervous centres not yet well defined, and death ensues from debility, progressive wasting, and exhaustion. Consequently tonic treatment is indicated—iron, strychnine, arsenic, and phosphorus may be administered singly or in some of their numerous forms of combination, Easton's syrup being one of the best. The diet should be chiefly nitrogenous, and all saccharine and starchy food should be withheld. There is no objection to the administration of dry sherry in moderate quantity. Theoretically, peroxide of hydrogen and permanganate of potash have found favour in the treatment of glycosuria. Two or three grains of codeia, especially in combination with about half a grain of extract of belladonna, most markedly diminish the amount of the urine secreted, while these agents do not, however, diminish the specific gravity. Antipyrin is said to diminish the amount of sugar.

Simulated Glycosuria.—For purposes of deception in the case of hospital patients and others, glycosuria is not unfrequently simulated by the addition of cane-sugar to the urine. This fraud is easily detected, as such urine does not reduce Fehling's solution. The cane-sugar is usually added in excess, and the density of the urine is thus suspiciously increased (1070 and beyond). By heating this urine for a few minutes with a dilute acid, the cane is transformed into grape sugar, and Fehling's test may be applied. Again, the saccharimeter in the former case shows a right deviation, while the latter is levogyrate.

Sometimes grape-sugar (raisin) is added. In this case the fraud is more difficult of detection. Grape-sugar as existing in commerce is never chemically pure, and contains products intermediate between grape-sugar and dextrine, possessing a right rotation. In a case of genuine glycosuria, the results obtained by chemical and optical analysis vary but to a trifling degree,

while if grape-sugar has been added to the urine, the chemical method gives a higher result than the optical.

LEVULOSE, LACTOSE, INOSITE.

Levulose, or Invert Sugar ($C_6H_{12}O_6$), is sometimes found in the urine of diabetic patients. Its behaviour with reagents is almost identical with that of glucose. It is uncrystallizable, and deviates the plane of polarization to the left. It undergoes fermentation, but less readily than glucose. A saccharine urine with left rotation usually points to levulose. It must be borne in mind in this connection that the ingestion of chloral, camphor, and benzene gives to the urine a like property, while it reduces copper in alkaline solutions. Levulose is also indicated when Fehling's solution shows a greater proportion of sugar than polarization does.

Lactose, or Sugar of Milk (*Saccharum Lactis*, B.P.— $C_{12}H_{22}O_{11}$), as already noted, usually exists in the urine of pregnant and nursing females, and children at the breast. It is the sweet principle of the milk of animals, and does not undergo the alcoholic or vinous fermentation. It crystallizes in oblique prisms, soluble in water, but insoluble in alcohol and ether. Its solutions are dextrogyrate. It resembles grape-sugar in reducing alkaline solutions of copper with precipitation of suboxide, but it has no effect on Barfoed's reagent.* In order to prove its presence in urine it must be separated in the following manner: The urine is precipitated by a mixed solution of acetate of lead

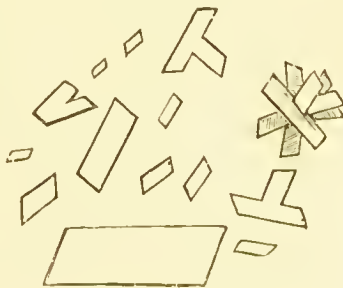


FIG. 37.—LACTOSE.

and ammonia. The precipitate obtained is decomposed by sulphuretted hydrogen, and the hydrochloric acid liberated is neutralized by oxide of silver. After filtration the excess of silver is precipitated by carbonate of baryta. A crystalline mass is obtained by further filtration and concentration, which can be

* A weak solution of acetate of copper with 1 per cent. of acetic acid.

crystallized after washing with dilute alcohol. It is distinguished, as already indicated, by reducing 'Fehling,' and having no influence on Barfoed's reagent.

Inosite ($C_6H_{12}O_6 + 2H_2O$).—This substance is isomeric with glucose, and is found in the muscles, in the lungs, in the kidneys, liver, brain, etc. It sometimes co-exists with glucose in the

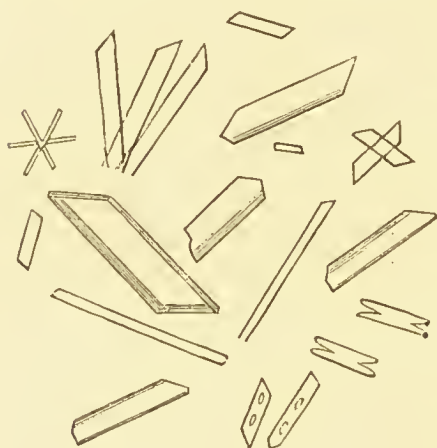


FIG. 38.—INOSITE.

urine. It crystallizes in a rhomboidal form or prismatic needles. It is very soluble in water, but is insoluble in ether or absolute alcohol. It does not undergo alcoholic fermentation, but in contact with proteid animal matter it is converted into lactic and butyric acid. It does not become brown on boiling with liquor potassæ, it does not reduce Fehling's solution, and is without action on polarized

light. It is precipitated by basic acetate of lead. If a solution of inosite with nitric acid be evaporated to dryness on a platinum plate, the residue moistened with a little chloride of ammonium and chloride of lime, and carefully again evaporated, a beautiful rose coloration is produced (Scherer).

Mercuric nitrate solution gives with neutral solutions of inosite a yellow precipitate. By carefully evaporating the liquid the precipitate becomes more or less red, the colour disappearing on cooling. As albumen behaves similarly, care should be taken that the urine contains none of it. If sugar be present, the coloration is black; it also must be removed.

Analysis.—The urine is treated by neutral acetate of lead, which separates the sulphates, chlorides, etc., boiled and filtered. The filtered liquid is then evaporated to about a fourth; basic acetate of lead is again added, and a precipitate is obtained containing inosite. This precipitate is collected, washed with distilled water, then suspended in a fresh quantity of water, and

decomposed by sulphuretted hydrogen. The resulting sulphide of lead is separated by filtration, the filtered fluid is concentrated by evaporation, and the inosite precipitated by the addition of concentrated alcohol. After repose the deposit acquires more or less coherence. It is then redissolved in distilled water, evaporated, a little concentrated alcohol or ether added, and crystallization allowed to take place. The tests of Scherer and Gallois may then be applied.

Pathological Significance.—Inosite is found in the urine in most cases of polyuria. In thirty cases of diabetes and twenty-five of albuminuria, Gallois found inosite in seven—viz., in five of the former and two of the latter.

CYSTINE.

Cystine ($C_6H_6NS_2O_4$), first discovered by Wollaston in 1810 is sometimes found in a state of solution in the urine. It is most frequently found in a sedimentary form, often in combination with urate of soda, and in the majority of cases in the form of a calculus. Cystine is found in the substance of the liver and kidneys. It is a remarkable fact that it is sometimes found in several members of the same family, so as to constitute a distinct diathesis allied to the rheumatic.

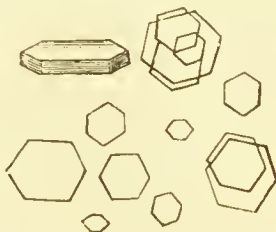


FIG. 39.—CYSTINE.

Characters and Properties.—Cystine is a substance rich in nitrogen and sulphur. It is colourless, inodorous, and entirely transparent, and crystallizes in hexagonal scales. It is insoluble in water, alcohol, and ether, but readily soluble in ammonia, unlike the somewhat similar crystals of uric acid. It is likewise soluble in solutions of potash, the mineral acids, and oxalic acid, but insoluble in tartaric and citric acids. Heated on platinum it decomposes, evolving a foetid odour, and burns with a greenish-blue flame; heated on silver it causes a black or brownish stain of sulphide of silver. Cystine dissolves with the aid of heat in nitric acid; on the solution being evaporated, a reddish residue is left, which is not affected by caustic alkalis.

The presence of sulphur in cystine can be demonstrated by

solution in caustic soda, boiling for a few minutes, and adding a solution of oxide of lead: a black precipitate of sulphide of lead is obtained. The presence of nitrogen is shown by heating in a tube with a fragment of potash, when ammonia is evolved.

If cystine be dissolved in a strong solution of boiling potash, and a weak solution of nitro-prussiate of soda be added, a beautiful violet colour results. Urine containing cystine is characterized by its pale colour, tendency to alkalinity, and, during putrefaction, by the exhalation of an odour of sulphuretted hydrogen. If it contain much cystine the specific gravity is high.

Analysis.—To separate cystine dissolved in urine it is precipitated by acetic acid; the precipitate is collected on a filter, and dissolved by means of ammonia. By evaporation of the ammoniacal solution, or the addition of acetic acid, the cystine crystallizes in characteristic hexagonal scales, when the tests above mentioned may be applied.



FIG. 40.—TYROSINE.

TYROSINE AND LEUCINE.

Tyrosine ($C_9H_{11}NO_3$) and leucine are products of imperfect oxidation of albuminoid substances.* Both bodies are found normally in the liver, pancreas, lymphatic glands, etc., and wherever albuminous substances undergo putrefaction, as in old cheese.

Properties.—Tyrosine is sparingly soluble in cold water; it dissolves in 150 parts of boiling water, and is insoluble in ether. It

is difficult of solution in pure alcohol, but dissolves in ammoniacal alcohol, in acids, and caustic alkalies and carbonates.

* Vide 'Lectures on Bright's Disease,' by Author, p. 68.

It does not sublime when heated, being thus distinguished from leucine, and decomposes with an odour of burnt horn. It crystallizes in the form of elongated silky needles, uniting in radiate form (Fig. 40).

Evaporated on a platinum plate, it assumes an orange colour, and leaves a deep yellow residue, transformed into red by soda. Evaporated anew, the liquid becomes brownish-black (Scherer's reaction). If nitrate of mercury be added to a boiling solution of tyrosine, a flaky red precipitate is obtained, and the solution assumes a rose colour. If a few drops of tyrosine be mixed with a few drops of concentrated sulphuric acid in a capsule, gently heated, and a little water be added, a liquid is obtained which, neutralized with carbonate of baryta, gives with neutral perchloride of iron a beautiful violet-red coloration.

Pathological Significance.—Tyrosine does not exist in healthy urine. With leucine, it is found in the urine in cases of yellow atrophy of the liver, typhus fever, and small-pox, and in cases of poisoning by phosphorus, where the blood is suboxidized. In pernicious anæmia it has also been found, and here there is likewise suboxidation from a deficiency of red corpuscles. Microscopic examination most easily reveals the presence of tyrosine and leucine.

Leucine ($C_6H_{13}NO_2$), like tyrosine, is derived from organic constituents rich in nitrogen. It is found, in like manner, normally in the liver, pancreas and spleen.

Properties.—Pure leucine crystallizes in the form of successive thin plates. When impure, as found in clinical research, it presents the form of

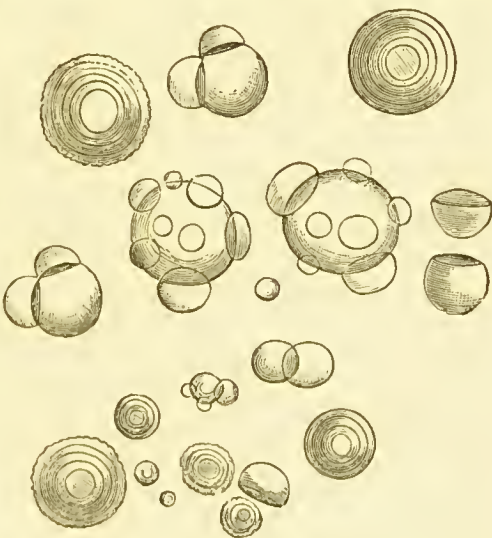


FIG. 41.—LEUCINE.

small spherules, usually coloured, striated, and with jagged projections. Gently heated to 170° , it sublimes in a flaky cloud, and is thus distinguished from tyrosine. If the temperature be elevated to 180° , the leucine is decomposed, leaving a liquid from which amylamine ($C_{10}H_{13}N$) crystallizes out on cooling. Evaporated on a platinum plate with nitric acid, leucine leaves a spare, colourless residue, which, treated with a few drops of caustic soda, dissolves on being heated, giving a colourless or yellow fluid, which, again, on evaporation, forms an oily globule, which rolls about, and does not tarnish the platinum.

Pathological Significance.—Leucine exists in the urine in cases of yellow atrophy of the liver.

Analysis.—Tyrosine and leucine are usually found in the urine in the state of solution. Leucine is always in smaller quantity than tyrosine. To separate these constituents from the urine, if it be albuminous, the albumen must first be removed by coagulation and filtration. The filtrate is then precipitated by basic acetate of lead. This is again filtered, and the excess of lead removed by a current of sulphuretted hydrogen. Filtration is again resorted to, and the filtrate evaporated. After a brief repose tyrosine deposits. This deposit may again be dissolved in boiling water, allowed to crystallize, and examined microscopically, or with the above-mentioned reagents.

To separate leucine, the fluid from which the tyrosine has been obtained is evaporated to dryness, treated at first with cold and then with boiling alcohol. The alcoholic solution thus obtained is evaporated to a syrupy consistence, and after a short time's repose the leucine separates in its characteristic spherical form. The leucine is yet impure, and should be purified as follows before applying chemical tests: Dry the leucine between two sheets of filter paper, dissolve in ammoniacal solution, and precipitate the solution by neutral acetate of lead. Filter; suspend the precipitate in water, and decompose by sulphuretted hydrogen. Concentrate the filtered fluid by evaporation, and set aside for crystallization. In the form of a sediment tyrosine is recognised in the following manner: The sediment is collected on a filter, washed with water, and dissolved in ammonia with the addition of a little carbonate of ammonia. Crystallize by evaporation, and examine microscopically and chemically.

ACETONE.

History of Acetone—Properties—Chautard's Test—Orthonitrobenzaldehyde Reaction—Extraction of Acetone from Urine—Quantitative Analysis—Pathological Significance—Various forms of Acetonuria.

Acetone (C_3H_6O) is often found in diabetic urine (acetonuria), being first discovered in this fluid by Peters.* It is most usually found in the urine in the advanced stages of diabetes. It is also found in a considerable number of febrile affections, as in scarlatina, pneumonia, and cancerous affections of the digestive organs; and in leucocythæmia, pernicious anæmia, Addison's disease, etc. Urine containing acetone emits a peculiar odour like that of chloroform, is usually scanty, and of high specific gravity. In proportion to the abundance of acetone, that of glucose is inversely diminished. The breath also has the characteristic smell of acetone, especially in the last stages of diabetes. According to Jaksch, acetone exists in feeble quantity in normal urine (0.01 or more in twenty-four hours).

Properties.—Acetone is a clear liquid of a density of 0.814, boiling at $56^{\circ} C.$, inflammable, and of an agreeable odour (like acetic ether), and mixes in all proportions with alcohol and ether. Submitted to the successive influence of a concentrated solution of iodine in iodide of potassium and of caustic soda, it forms iodoform, which separates in microscopic hexagonal tablets, or in stars of six arms, of a yellow colour and disagreeable odour (Lieben's reaction). Alcohol, according to Jaksch, gives the same reaction, but with it the iodoform forms much less rapidly than with the acetone.

Acetone may be obtained by the distillation of acetate of soda, or a mixture of acetate of lead and of lime. The condensed liquid is brought under the action of chloride of lime, and then distilled on a water-bath. The distillate is collected. This is again brought in contact for several hours with lime, then distilled anew, collecting only what passes at $56^{\circ} C.$ Acetone combines with bisulphite of soda, forming a crystalline compound.

In 1864 Gerhardt† demonstrated that certain urines containing

* *Vierteljahrsschrift für de Pract. Heilkunde*, Prague, 1857.

† Gerhardt, *Wiener Medicinische Presse*, vol. iv., p. 28.

sugar were coloured red by the addition of perchloride of iron. Until recently it was believed that this coloration was due to the acetone contained in the urine; and certain of the phenomena of the comatose state, in cases of diabetes, were attributed to this principle. Von Jaksch subsequently arrived at different conclusions from Gerhardt, and he proved that the reaction described by Gerhardt was produced by acetylacetic acid, while with regard to the acetone, it was necessary for its detection to employ a special method. Urine containing sulphocyanide of potassium is also coloured red by perchloride of iron.

The reddish-brown colour produced by sulphuric acid in urine containing acetone is also equally fallacious, as it is likewise produced in urines which do not contain this principle. The same applies to the reaction of Lieben. The following tests are, however, reliable.

Chautard's Test.*—Dissolve 0.25 gramme of fuchsine in 500 grammes of water, through which pass a current of sulphurous acid until the yellow colour disappears. This solution (sulpho-rosanilinic reaction) may be kept indefinitely in stoppered bottles. With a tenth part of acetone, this reagent gives an intense violet colour, with $\frac{1}{100}$ th a similar colour, and with $\frac{1}{1000}$ th a sufficiently appreciable colour. When the amount of acetone is small, 200 c.c. of the urine may be distilled, and the first 15 c.c. of the distillate may be tested.

Orthonitrobenzaldehyde Reaction.—This test, of great sensibility, has been recommended by Baeyer and Drewsen. A few crystals of *orthonitrobenzaldehyde*, which, being explosive, must be carefully handled, are boiled with a little water, and the solution allowed to cool. To the first products of the distillation of the urine, rendered alkaline with a soda solution, some of the above solution is added. After about six minutes, if the urine contain acetone it becomes yellow, then green, and finally precipitates indigo. If the acetone be only in small quantity, the yellow fluid is to be agitated with chloroform, and after a short time the indigo colour ensues.

Otherwise, prepare ready for use a 5 per cent. solution of nitro-prussiate of soda and a 30 per cent. solution of caustic

* *Bulletin de la Société Chimique*, t. 45.

potash. To the first portion of the distillate a few drops of each of these solutions are added; boil, and add a few drops of acetic acid by pouring gently along the tube wall so as to prevent admixture. At the point of junction of the fluids a beautiful red colour is produced. The successive addition of the foregoing solutions even without acetic acid causes a pronounced red colour with acetone. If then acetic acid be added and the fluid boiled, the red colour is changed into green. According to Weyl, creatinine gives the same reaction.*

To extract Acetone from the Urine.—Von Jaksch recommends that almost a litre of this fluid should be acidulated with hydrochloric or tartaric acid, ether added and distilled. The acidulation prevents cloudiness, and the passing of carbonate of ammonia into the distillate. To the latter is added a small quantity of iodine, dissolved by means of iodide of potassium, and finally caustic potash. The result is, according to the amount of acetone, either a precipitate or an opacity due to the formation of iodoform (Lieben's reaction). Iodoform is recognised by its odour, by its volatilization on being heated, and by its crystalline form. In order to obtain it in this form the liquid containing the iodoform is agitated with ether, which spontaneously evaporates, and the crystals subside.

Quantitative Analysis of Acetone.—Salkowski† and Taniguti employ the following process: To 300 c.c. of urine add 10 c.c. of concentrated sulphuric acid, and distil. To the distillate add soda or potash lye, then the iodine solution, and set aside for twenty-four hours. Filter, collect the iodoform, and weigh.‡

Pathological Significance.—It has been observed that the breath of diabetic patients is characterized by a vinous odour. This has in recent years been proved to be due to the presence of acetone (acetonæmia) in the blood. According to Lieben,§ acetone exists to the extent of about 1 centigramme in the urine of twenty-four hours; but in certain pathological states the

* Acetone reduces Fehling's Solution.

† *Zeit. für Physiol. Chemie*, xiv., 1890, Heft 5.

‡ *Vide Annal. des Mal. des Organ. Genito-Urin*, No. 9, 1892.

§ Lieben, *Annales der Chemie und Pharmacie*, p. 236, 1870.

quantity amounts to as much as 50 centigrammes per diem. This pathological condition, to which the name of hyper-acetonuria has been given, was observed under four different conditions: First, fever, from whatever cause; secondly, in diabetes; thirdly, in certain cases of cancer; fourthly, in patients suffering from an affection to which Kaulich and Cantani gave the name acetonæmia.

First Form.—If in any patient the fever attains to a high degree, hyper-acetonuria appears. The most varied affections present this phenomenon.

Second Form.—Independently of numerous cases of diabetes in which acetone is not in excess, there are two varieties: First, the cases in which acetone is in excess; secondly, the cases in which acetone is in excess, and in which the urine gives Gerhard's reaction. In these cases the affection is grave, and death is usually ushered in by coma.

Third Form.—Acetonuria occurs in certain cases of carcinoma. The cause is unknown.

Fourth Form.—In the acetonuria of Kaulich and Cantani acetone is found in excess in the urine. Perchloride of iron in these cases invariably gives a red reaction. Gerhard's reaction is seldom given in grave diabetic acetonuria. Acetone and acetylacetic acid are far from being independent in every case. Siefert* believes that the appearance of acetone in the urine is due to the ingestion of alcohol. Like Jaksch, he observed the reaction in various febrile disorders, and distinguished certain new features of it, differentiating it from other reactions of a similar kind. The constituent thus discovered in the urine would be, according to this authority, not acetylacetic acid, but acetylacetate of ethyl, which in decomposing gives origin to acetone, the accumulation of this substance in considerable quantity in the organism exercising, according to Siefert, a depressing action on the cerebral functions.

Brieger has demonstrated that it required at least 2 grammes of acetylacetate of ethyl to a litre of urine to obtain the reaction of Gerhard. In another series of experiments, 20 grammes of

* *Physikalisch-Medicinische Gesellschaft, Würzburg, vol. xvii., No. 4, 1882.*

acetylacetate of ethyl per diem were given to perfectly healthy men and to a diabetic patient without Gerhard's reaction having been obtained.*

MELANINE.

In certain cases of melanosis this pigment appears in the urine, which when emitted is clear, but gradually becomes of a deep brown, or even black, colour.

Ordinarily melanine exists in solution in the urine, but sometimes in the form of a brownish or black sediment, recognisable by microscopic examination. Melanine may possess a diagnostic significance, when the melanosis is beyond the reach of examination by eye or touch. It may disappear from the urine when the disease is arrested, or remain stationary. Oxidizing agents, such as chromic acid and fuming nitric acid, transform the principle melanine, causing gradually with the first and immediately with the second a black coloration. According to Zeller, the most delicate test for melanine is bromine water. With melanine it gives at first a yellow precipitate, which gradually blackens. Urobiline gives a yellow precipitate with same reagent, but it does not blacken.

DIVERSE ACIDS.

The following acids are occasionally found in the urine :

Lactic Acid ($C_3H_6O_3$) is found in the urine in cases of poisoning by phosphorus, yellow atrophy of the liver, and *mollities ossium*. It is probably derived from the fermentation of saccharine and amylaceous substances. Formic Acid ($HCHO_2$), so called from the fact that it is ejected from the red ant when irritated, is found in the urine in cases of leucocythæmia. Valerianic Acid ($HC_5H_9O_2$) is found in the urine in cases of typhus fever, small-pox, and yellow atrophy of the liver. Acetic ($HC_2H_3O_2$) and Propionic Acid (C_2H_5COOH) are found in cases of diabetes after the urine has undergone fermentation. Lehmann found Butyric Acid ($HC_4H_7O_2$) in the urine of females after childbirth.

* *Vide* 'Considerationes sur le diabète Acetonémique,' par J. Cornillon et A. Mallat (*Le Progrès Médical*, April, 1886).

BILE ELEMENTS.

Bile Elements—Mucine of Bile—Biliary Pigments: Bilirubine, Biliverdine, Biliprasine, Bilifuscine, Bilihumine—Detection of Colouring Matter of Bile in Urine—Gmelin's Reaction—Analysis—Rosenbach's Modification of Gmelin's Test—Huppert's Reaction—Bile Acids: Choleic or Taurocholic Acid, Glycocholic Acid, Cholalic Acid—Reaction of Bile Acids (Pettenkofer's Reaction)—Cholesterine—Analysis—Pathological Significance.

When secreted by the liver bile is a yellow fluid, of a density varying from 1020 to 1035. According to the length of time which it remains in the gall-bladder, it becomes of a deeper brown colour. It contains no albumen. On being treated with alcohol, the mucine which it contains is precipitated. Of all the fluids of the system it is the densest, a tenth of its weight consisting of solid matter—chiefly biliary pigments, acids, mucine, and cholesterine.

Mucine of Bile.—In addition to its acting as a reservoir for bile, the gall-bladder adds to the bile its special secretion—mucine. Bile as it exists in the hepatic canals does not, therefore, contain mucine. This constituent may be separated from bile by treating it with four or five times its volume of alcohol.

Biliary Pigments.—The colouring pigments of the bile are:

Bilirubine ($C_{16}H_{18}N_2O_3$).

Biliverdine ($C_{16}H_{18}N_2O_4$).

Biliprasine ($C_{16}H_{22}N_2O_6$).

Bilifuscine ($C_{16}H_{20}N_2O_4$).

Bilihumine.—Atomic composition not yet determined.

All the four latter of this group of substances appear to be derived from the former by oxidation.

Bilirubine ($C_{16}H_{18}N_2O_3$) is found in the bile in small quantity in combination with alkaline bases. It is almost the sole constituent of certain biliary calculi. It may be removed from bile or bilious urine by the addition of hydrochloric acid and agitation with chloroform. It may be obtained from calculi containing it by first treating them with ether to remove the fatty matter and cholesterine which they contain; the salts are then dissolved out by boiling water, and the residue treated with hydrochloric acid and chloroform, in which the

bilirubine is dissolved. This solution by evaporation deposits an impure bilirubine. On this being treated with alcohol and ether, bilifuseine and fatty matter are removed; the remainder may then be crystallized from chloroform. Bilirubine appears in the form of an amorphous orange-coloured powder. Crystallized from the chloroform solution, it forms rhomboidal microscopic prisms. It is insoluble in water, sparingly soluble in alcohol and ether, very soluble in chloroform, benzene, and bisulphide of carbon. The solutions are

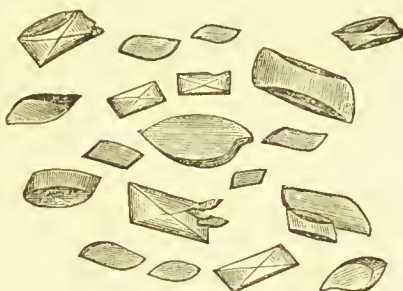


FIG. 42.—BILIRUBINE.

yellow, and are precipitated by soluble metallic salts, the bilirubine forming combinations with the oxides of the metals, which are insoluble in water and chloroform. Bilirubine is soluble in caustic alkalis, in which, by the absorption of oxygen, it is converted into biliverdine.

Biliverdine ($C_{16}H_{18}N_2O_4$) is a product of the oxidation of bilirubine. It may be obtained by exposure of an alkaline solution of bilirubine to the air in a wide-mouthed bottle, and shaking from time to time. Finally it transforms into biliprasine. When the green colour due to oxidation has ceased, the solution is precipitated by hydrochloric acid. The precipitate is washed with boiling alcohol, which dissolves the biliverdine alone, from which it separates on evaporation as a greenish residue. Biliverdine is amorphous, of a deep green colour, insoluble in water, ether, and chloroform, but soluble in alcohol and alkalis, the solution being of a green colour.

Biliprasine ($C_{16}H_{22}N_2O_6$) is derived from biliverdine by the addition of two molecules of water. It is found in small quantity in biliary calculi, from which it may be extracted by treatment with water, hydrochloric acid, ether, and chloroform, so as to remove the substances soluble in these agents, the biliprasine being left as a residue. From this residue it is dissolved by alcohol, in which it is easily soluble, the solution being of a green colour, becoming brown by the addition of

ammonia. It is soluble in alkalies, and the brown solution is converted into green by the addition of acids. It is insoluble in water, ether, and chloroform.

Bilifuseine ($C_{16}H_{20}N_2O_4$) is a deep-brown powder, amorphous, almost insoluble in water, ether, and chloroform, but readily soluble in alcohol, ammonia, and soda, giving a deep-brown solution. It accompanies bilirubine in biliary calculi, and is dissolved from them, or from bile, when they are treated with chloroform and hydrochloric acid. It separates from bilirubine on being treated with alcohol, in which bilirubine, as we have seen, is insoluble.

Biliumine, a constituent found only in biliary calculi, is of a brown earth (*humus*) colour. Its composition is not yet determined. It remains as a residue when biliary calculi have been successively treated with water, alcohol, ether, chloroform, and hydrochloric acid. It is therefore insoluble in these agents. It is soluble in caustic soda and ammonia, and is precipitated from their solutions by hydrochloric acid.

Other products of the oxidation of bilirubine, such as bilicyanine or eholoverdine, and choleteline have been described.

Detection of Colouring Matter of Bile in the Urine.—

The mere aspect of bilious urine affords an indication as to the particular pigment present. Thus, if bilirubine predominates, the urine is yellow; if biliverdine, it is greenish. Such urine stains linen or blotting-paper immersed in it, and on being agitated gives a yellow froth. Urine passed after the ingestion of senna, rhubarb, and santanine presents the same peculiarity, but these may be distinguished by their characteristic reactions.

Gmelin's Reaction.—If to a solution of the foregoing constituents a little nitric acid be added, the liquid at first assumes a green colour, then blue, subsequently violet and red; and at the end of some seconds, if the acid be in excess, the red colour disappears, and the liquid becomes yellow. If a solution of the pigments be poured on nitric acid so as to prevent mixing of the fluids, the various colours appear simultaneously in superposed layers, the green being uppermost. The green colour alone is characteristic of the bile pigments.

Analysis.—Urine containing bile pigments is of a more or less

yellow colour; or it may be brownish, reddish-brown, or green, according to the predominating pigment. When the urine is yellow, bilirubine predominates; when it is green, biliverdine. Linen and blotting-paper are stained by such urine, corresponding to the colour, and agitation causes a coloured froth. Into a conical vessel gently pour two or three c.c. of nitric acid which has been more or less exposed to air, then, by means of a pipette, place over it, without admixture, a little of the urine. If it contain bile pigments, there will be produced at the point of contact of the two liquids a green ring of more or less thickness, and below this violet, red and yellow rings. Indican gives with nitric acid the blue and red coloration; but the green is characteristic of bile pigments.

In order to identify bile pigments in sediments, such as urates, dissolve these sediments in carbonate of soda and test as above. The presence of albumen does not interfere with this reaction, if the colouring matter be not in very minute quantity.

Rosenbach's Modification of Gmelin's Test.—Filter a given quantity of urine, then moisten the inner surface of the filter, still moist, with nitric acid. Concentric zones of green, blue, violet, and reddish-yellow then appear on the paper if bile salts be present.

Bilious urine mixed with a drop of nitrate of soda solution and a little dilute sulphuric acid assumes a beautiful green colour. After some time the green disappears, and is replaced by yellow, without passing through the stages of red and blue.

If a few drops of tincture of iodine be added to bilious urine, at the point of contact of the fluids a beautiful emerald-green colour appears. Iodine water produces the same result.

Bilirubine may be isolated from bilious urine in the following manner: Into a small flask pour 100 c.c. of urine and 10 c.c. of chloroform, and gently mix the two liquids. Invert the flask, still closed, gently open the mouth of the flask, and allow the chloroform emulsion alone to pass out, and apply *Gmelin's* reaction.

Huppert's Reaction.—Add to the urine a little ammonia and chloride of lime. If it contain bile pigment, a precipitate containing bilirubine is formed. This precipitate may be separated

by filtration, washed, and, while still moist, treated with strong alcohol containing sulphuric acid. On being heated the liquid will become of an emerald-green or greenish-blue colour.

Ehrlich recommends the following process to identify bilirubine alone: Mix a given quantity of urine with an equal volume of dilute acetic acid, and then add, drop by drop, a solution of sulphodiabenzol (one part of sulphanilic acid in 1,000 parts of water, with 15 c.c. of hydrochloric acid and 0.1 nitrate of soda). If the urine contains bilirubine, the mixture assumes the violet colour characteristic of this constituent. When the bile pigments are decomposed, exist only in small quantity, or when the urine contains indican, these processes are inapplicable. In such cases the bile pigment must be isolated; to effect this render the urine alkaline by soda lye, then mix with chloride of barium or of lime, when a yellow precipitate forms. Filter, and boil the precipitate with alcohol containing a few drops of sulphuric acid, when the liquid assumes a beautiful blue colour.

BILE ACIDS.

According to Dragendorff, biliary acids are contained in normal urine in the proportion of 0.8 gramme to 100 litres.* These acids are, however, most frequently found in pathological states, united to the bile pigments. The two acids which exist in human bile under the form of soda salts, viz., *choleic* or *taurocholic acid*, and *cholic* or *glycocholic acid*, are combinations of a third acid, *cholalic acid*, with *taurine* on the one hand, and *glycochole* on the other.

Choleic or Taurocholic Acid ($C_{26}H_{45}NSO_7$) is a white amorphous powder, soluble in water, alcohol, and chloroform, and insoluble in ether. Its solutions are dextrogyrate. Boiled with potash or hydrochloric acid for some hours, it is resolved into cholalic acid and taurine.

Glycocholic Acid ($C_{26}H_{43}NO_6$) crystallizes in fine needle-prisms, which are colourless, and do not contain sulphur, by

* *Annal. des Mal. des Organ. Genito-Urin.*, No. 8, 1892, p. 647.

which they are distinguished from choleic acid. It dissolves with difficulty in cold, but readily in boiling, water and in alcohol. It is sparingly soluble in ether. On boiling with potash or hydrochloric acid it is resolved into cholalic acid and glycochole.

Cholic Acid ($C_{24}H_{40}O_5$) exists in the urine only in combination with taurine and glycochole, with which it forms the two preceding acids. It crystallizes in four or six sided prisms. It is insoluble in water, very soluble in alcohol, sparingly soluble in ether. Its solutions are dextrogyrate.

Boiled with mineral acids, it loses water and is transformed into dyslusine ($C_{24}H_{26}O_3$).

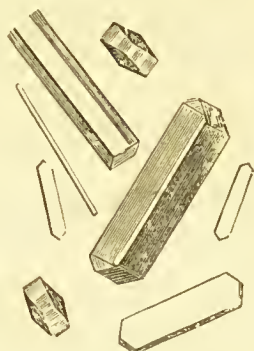


FIG. 43.—GLYCOCHOLIC ACID.

Reaction of Bile Acids (*Pettenkofer's Reaction*).—This is the test most frequently employed, and is as follows: To a solution of the foregoing acids add a few drops of a weak solution of sugar, a little concentrated sulphuric acid, and heat to a temperature not exceeding $60^{\circ} C.$, when a violet-purple colour is obtained. Neukomm renders the reaction more delicate by the following procedure: Mix in a porcelain capsule a solution of bile-acids with a drop of dilute sulphuric acid, and a drop or two of sugar solution; heat on a water-bath, when a beautiful violet-purple colour appears.

The bile-acids may be isolated as follows: Evaporate a considerable quantity of urine on a water-bath almost to dryness. Then extract by alcohol, and with precaution evaporate anew. Dissolve the residue in a few drops of water and apply Pettenkofer's test. If the urine contain albumen it must be separated.

Cholesterine.—The presence of cholesterine in the urine is very rare. It is found in cases of chyluria and fatty degeneration of the kidney, sometimes in the form of a sediment, and as a constituent of certain calculi.

Cholesterine ($C_{25}H_{43}HO$), crystallizes in rhomboid scales, or in the form of fine needles. It is insoluble in water, dilute acids, alkalis, and cold alcohol, but soluble in boiling alcohol, ether, and chloroform. It may be extracted from gall-stones by boiling

alcohol, from which it deposits on cooling. If a little cholesterol be dissolved in 2 c.c. of chloroform, and about the same volume of sulphuric acid be added, the liquid agitated, and then allowed to repose, the supernatant chloroform solution is found at first to be of a blood-colour, then cherry-red or purple, while the sulphuric acid becomes intensely green. If a little of the chloroform solution be put in a porcelain capsule, it undergoes rapid coloration from blue to green and yellow.

Analysis.—To identify cholesterol in the urine, agitate with ether, decant the fluid, and evaporate. Treat the residue with

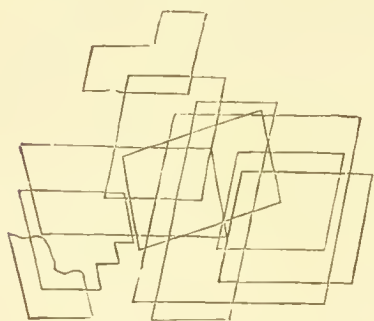


FIG. 44.—CHOLESTERINE.

alcohol, add a little potash, and boil for some time on a water-bath. Treat the residue with water, and agitate with ether. Evaporate the ethereal solution, redissolve the crystals in boiling alcohol, filter, and allow crystallization to take place.

Add, drop by drop, strong sulphuric acid, or nitric acid and ammonia, to an ethereal solu-

tion of cholesterol in a porcelain capsule, and a red coloration is the result. A solution of iodine and a drop or two of sulphuric acid causes a greenish-blue coloration, changing to violet.

Pathological Significance.—When bile is prevented from flowing into the intestines from any cause whatever, such as active or passive hyperæmia of the liver, as from alcohol, obliteration of the biliary canals by calculi, catarrhal inflammation of these canals, extending to the lobules of the liver, inflammation of the gall-bladder, its compression by a tumour, interstitial hypertrophy, as in phosphorus-poisoning, œdema of Glisson's capsule, etc., the bile is reabsorbed, and passes into the circulation. This is made manifest by the yellow colour imparted to the various tissues of the body, and notably the conjunctiva. Bile elements are then eliminated by the kidney, and are found in the urine.

FATTY MATTER.

Lipuria, Chyluria, Galacturia.*—Cases of chyluria may be grouped as follows :

Chyluria properly so called, when it depends or not on parasites. The parasitic form of chyluria is found in tropical climates, and is caused by a round worm, the *Filaria sanguinis hominis*. The passing of the parasite from the blood to the kidney causes chyluria and hæmaturia. The urine necessarily contains albumen in—

Advanced Fatty Degeneration of the Kidney, or of other portions of the urinary tract, as in cases of phosphorus-poisoning. The bursting of an old abscess, and the consequent admixture of urine and pus may cause chyluria.

Phthisis, prolonged suppurations, and all grave constitutional diseases, may cause chyluria.

Chyluria has been observed after the ingestion of large quantities of aliment rich in fat, or after the experimental injection of oil into the bloodvessels. The fat presents itself under the form of more or less voluminous drops, which float to the surface (lipuria), or in a state of fine division, as in milk (galacturia). In the former case the urine appears as if it contained pus. In the case of pus, however, a deposit takes place, and a clear supernatant fluid remains, while the fatty urine retains its opacity.

Detection of Fat in the Urine.—On microscopic examination fat is observed in the form of fine granulations or small drops, of greater or less size, with dark contour, a brilliant centre, and very refractive. Chemically, the following reactions take place with fat: On being heated, a characteristic odour of acrolein is given off. On the addition of chloroform or ether, or sulphide of carbon, the urine becomes more or less clear. If the urine be poured on white paper, fatty stains may be observed. Lecithine and cholesterine, which are of a fatty nature, may also be found in the urine.

* *Vide* 'Annal. des Mal. des Orgs. Genito-Urin.,' No. 2, 1893, p. 124.

Pathological Significance.—Lipuria most frequently occurs in fatty degeneration of the kidney, in cases of poisoning by phosphorus, in phthisis, pyæmia, gangrene, acute atrophy, and fatty degeneration of the liver, carcinoma, and prolonged suppurations, especially in connection with bones and joints.

TUBE-CASTS.

By tube-casts are understood microscopic moulds of the uriniferous tubes of the kidney, resulting from inflammation of the organ. This inflammation may be chronic and incurable, as in advanced Bright's disease, or may be due to transitory

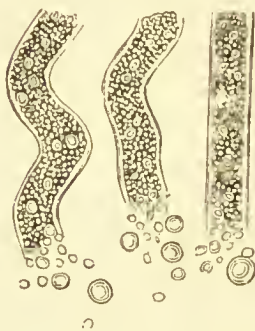


FIG. 45.—FATTY DEGENERATION OF TUBES FROM THE CORTICAL PORTION OF THE KIDNEY IN A CASE OF PHOSPHORUS POISONING (PHOSPHORIC STEATOSE).—*Ranvier*.

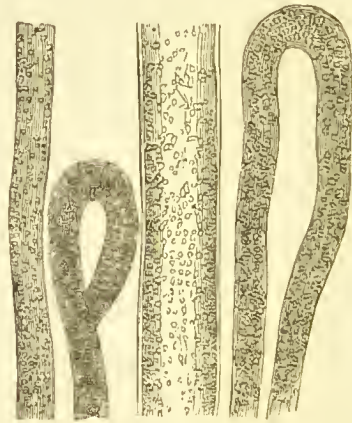


FIG. 46.—LONGITUDINAL SECTION OF THE TUBULAR SUBSTANCE OF THE KIDNEY IN A CASE OF ALBUMINOUS NEPHRITIS DUE TO POISONING BY PHOSPHORUS.

The Loops of Henle are more altered than the straight tube between them.

irritation of the organ from the elimination of certain irritants. These casts may be classified as: (1) *True cylinders or casts* (cylinders of destruction), comprising the following granular cylinders, viz., granular, granulo-fatty, fatty and mixed, amyloid tube-casts; (2) *Cylinders of exudation*—hyaline cylinders; (3)

Cylindroids—cylindroids, pseudo-cylinders, epithelial cylinders, hæmorrhagic cylinders, and spermatic cylinders.

Granular Cylinders.—This form of tube-casts presents an entirely granular aspect. They are less transparent than the amyloid and hyaline casts, and are generally larger. Sometimes they are short, and of considerable diameter. They present either a regular or irregular outline. Their extremities are rounded, like the finger-tip, or serrated. They are composed of the debris of red globules, of leucocytes, and of epithelial cells, which have undergone more or less degeneration.

Granulo-fatty cylinders may be regarded as the foregoing with fat globules superadded. They are found in Bright's disease. Pure **fatty granules** are found only in cases of poisoning by phosphorus. **Mixed cylinders** are combinations of the foregoing.

Amyloid Casts or Cylinders.—These cylinders are of homogeneous structure, are more refractive than hyaline cylinders, and are thus more defined in the microscopic field. They present a dull, waxy appearance. Ordinarily, they are short, and of greater diameter than the granular cylinders. Their contour is regular and smooth; sometimes notched. They are sometimes twisted on themselves in the form of a corkscrew. They resist the action of acetic acid, and are insoluble in heated urine, and in distilled water. Osmic acid imparts to them a dark-brown colour. Iodine colours them yellow, and carmine imparts to them a deep red colour. Sulphuric acid renders them green. These cylinders seem to be composed of an altered protoplasm of the uriniferous tube-cells.

Hyaline Cylinders.—These casts are homogeneous, pale, transparent, with ill-defined outline, flexible, of varying length, with defined or serrated extremities, and of a uniform diameter throughout their entire length as a rule. Sometimes they are broken into parts, and present the corkscrew appearance. Dilute acetic acid causes these cylinders to shrink, and they dissolve in strong acetic acid. Heated in the urine to 70° or 80° C., they dissolve, or heated to 30° or 40° C. in distilled water. They are soon destroyed in alkaline urine. The aspect

of these casts is frequently altered by the deposition on them of diverse elements from the kidney, such as granulations of urates, of phosphates, crystals of oxalate of lime, fatty drops, round cells, blood-corpuscles, etc.

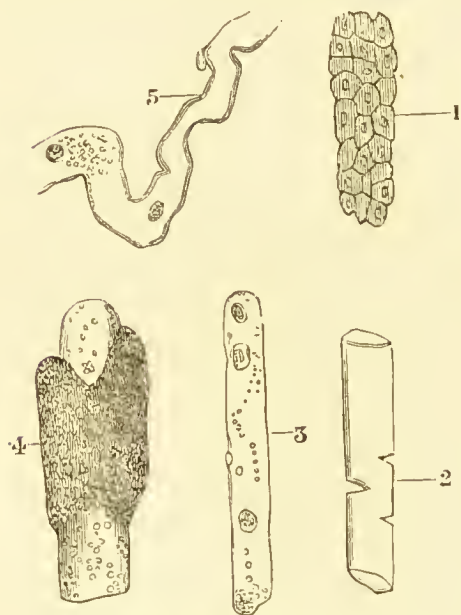


FIG. 47.—HYALINE CYLINDERS IN A CASE OF ALBUMINOUS NEPHRITIS.

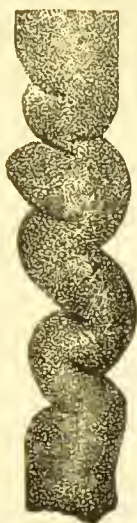
1, Desquamated Renal Cells; 2, Hyaline Cylinder with jagged edges; 3, Hyaline Cylinder with fragments of cells adhering, and occasioning a granular appearance; 4, Hyaline Cylinder covered with fatty granulations; 5, Hyaline Tube, of which the smaller portion seems to correspond to the *intermediate, or canal of union*.

Different salts, especially urates, are sometimes deposited in the uriniferous tubules, and are thus eliminated in the form of cylindrical masses. These may be readily distinguished by heating them on a glass slide, with a drop of hydrochloric acid, when crystals of uric acid will form.

Spermatic Cylinders.—These are composed of casts from the prostatic ducts, and are found in cases of chronic prostatitis

Cylindroids (Pseudo-Cylinders).—These elements (the *mucous cylinders* of Cornil and Ranvier) appear as simple filaments, or as 'ribbons' of irregular outline and unequal diameter. Their surface is striated, and their extremities denticulated. Their substance is transparent and colourless, and they are difficult to distinguish without the aid of staining agencies. Like other casts, their substance may have incorporated with it other elements, such as fat-drops, albuminous granulations, blood-corpuscles, leucocytes, epithelial cells, etc. They present a wavy appearance. Dif-

PLATE I.



1



2



3



4



5



6

- FIG. 1.—AMYLOID CAST TREATED WITH OSMIC ACID.
 FIG. 2.—COLLOID OR HYALINE CAST WITHOUT ANY REAGENT.
 FIG. 3.—COLLOID OR HYALINE CAST TREATED WITH OSMIC ACID.
 FIG. 4.—MUCOUS OR GRANULO-FATTY CYLINDER.
 FIG. 5.—FATTY CASTS TREATED WITH OSMIG ACID.
 FIG. 6.—GRANULO-FATTY CASTS.

[To face page 198.



and spermatorrhœa. These casts are hyaline, and resemble more or less renal cylinders.*



FIG. 48.—SPERMATOZOA AND PROSTATIC OR SPERMATIC CASTS.

Epithelial Cylinders.—These cylinders, according to Lecorché, are formed of small polygonal cells, which can come only from the ‘collector tubes’ of the kidney. They are composed of the desquamated surface of the straight tubes, and possibly of the descending limb of the loop of Henle. These casts are really very rare, and must not be confounded with mucous or granular casts, which present masses of epithelial cells. Their semeiological significance points to catarrhal irritation of the straight tubes.

Hæmorrhagic Casts.—These casts are composed of red and white blood globules, united by fibrine, and are of medium diameter. It is rare to find the red globules intact. Generally they present an annular form, and have lost their colouring matter.

Pathological Significance and Diagnostic Value.—The presence of tube-casts indicates inflammation more or less acute, acting especially upon the secretory structure of the kidney. This inflammation may be idiopathic, as in cases of Bright’s disease, or may be due to the action of irritants and poisons on

* *Vide* ‘Prostatic Casts,’ by D. Campbell Black, M.D. (*Lancet*, January, 1866), and ‘*Annales des Malad. des Organes Genito-Urinaires*,’ 1887, p. 329.

the renal structure, such as cantharides, strong diuretics, bile, phosphorus, etc., or secondarily, from the elimination of the 'poisonous débris' of such diseases as scarlatina, during the desquamative stage, small-pox, typhus, etc. Urinary cylinders are never wanting in acute nephritis and amyloid degeneration of the kidney. Casts are found in the urine of animals which have been covered with varnish and thus rendered albuminuric. Epithelial cylinders indicate desquamative nephritis. If pus corpuscles be found superadded, the prognosis will be less favourable, as a greater intensity of inflammation is thus evident. Blood-casts indicate intense inflammation, or effusion of blood into the parenchyma, or calyces of the kidney. Granulo-fatty cylinders give evidence of fatty degeneration of the kidney, especially if associated with epithelial cells—Bright's disease in its second stage. Amyloid cylinders point to sclerosis of the kidney. Hyaline and granular tubes, especially if abundant, indicate chronic Bright's disease—the small red granular kidney. They are formed in tubes denuded of epithelium. The urine is often in excess of the quantity secreted in health, and as the solid constituents of the urine are inadequately eliminated, the specific gravity of the urine is as low as from 1010 to 1005.*

In cases of cancer of the kidney the epithelial cells found in the urine are large, irregular, and present prolongations, or processes, with one or more nuclei.

According to Aufrecht,† tube-casts may be due to an exudation from the blood, or be the product of the renal epithelium. He cites the following facts in favour of the latter view: (1) In certain experiments he tried one ureter, when the renal epithelium was seen to contain masses of a hyaline substance, which subsequently made its way into the lumen of the tubules to form casts; (2) albuminuria may exist without casts; (3) there may be casts in the urine without albuminuria; (4) casts may be seen in the collecting tubes of a different colour, and of such a calibre that they could not pass through Henle's loops. The local origin of casts in the tubules has been undoubtedly shown in the cholera kidney and in that of scarlatinal nephritis.

* *Vide* Author's 'Lectures on Bright's Disease,' p. 62.

† *Centralb. f. inn. Med.*, May 12th, 1894.

CHAPTER V.

ABNORMAL CONSTITUENTS OF THE URINE—

Continued.

Inorganic Substances.

COMPOUNDS of ammonia are of frequent occurrence in the urine, and the carbonate of ammonia which, in the majority of instances, communicates its alkaline reaction to the urine, arises from the decomposition of urea, either before or after the emission of the urine.

Carbonate of Ammonia arises from the decomposition of urea under the influence of a special ferment. This decomposition takes place very rapidly in the presence of pus, or mucus, and especially when the temperature is elevated. Hence it is of frequent occurrence in cases of vesical catarrh.

Ammonic-Phosphate of Magnesia.—The formation of this compound is consecutive to that of the carbonate of ammonia. It forms in the bladder, and constitutes a form of gravel.

Phosphate of Soda and Ammonia.—In normal urine there exists a neutral phosphate of soda primarily; and in consequence of the presence of uric acid this salt is transformed into acid phosphate. When ammonia forms through the decomposition of urea, the acid phosphate absorbs it and transforms it into a double phosphate of soda and ammonia (NaNH_4PO_4).

Acid Urate of Ammonia ($\text{C}_5\text{H}_3(\text{NH}_4)\text{N}_4\text{O}_3$) is found invariably in urine which has become ammoniacal. This urate is not very soluble. On incineration it leaves no residue, and in order to distinguish it from uric acid the ammonia must be separated by treating with soda. It occurs under the form of more or less voluminous spheres, which often present longish spines. Urates

of lime and magnesia are also found, but more rarely, in the urine.

Analysis of Ammonia Salts.—Ammonia salts as existing in the urine are of two varieties, the one volatile at the ordinary boiling-point, the *carbonate of ammonia*; the other only decomposable at a more elevated temperature, and not evolving ammonia except through the agency of fixed alkalis.

The following is the process of Schloesing, modified by St. Claire Deville: Put a known quantity of urine, 50 to 100 grammes, for example, into a small capsule, suspended over a measured quantity of sulphuric acid, in a crystallizer whose base is immersed in mercury. The jar is closed by a plug, perforated by two tubes, the one curved, and closed by a stop-cock; the other a pipette, also closed by a stop-cock. The pipette is filled with milk of lime in graduated quantity. The stop-cock of the smaller tube is now opened, and a little air is admitted into the jar. The stop-cock of the pipette is now opened, and a little of the milk of lime is permitted to fall into the urine. In about forty-eight hours all the ammonia is evolved, and is absorbed by the sulphuric acid. An alkalimetric analysis will now show the quantity of ammonia evolved. Forty-nine grammes of the standard acid correspond to 17 grammes of ammonia; it is thus easy to calculate how much ammonia is represented by 10 c.c. of the standard acid. By means of caustic soda the amount of sulphuric acid remaining free may be determined. The difference represents the quantity of acid saturated by the ammonia of the urine, and consequently its proportion.

A more rapid process, and one sufficiently exact, consists in the decomposition of the ammonia salts by the hypobromite or hypochlorite of soda. For this purpose the *uro-azetometer* of Gautrelet-Vieillard may be employed. Sutton recommends the following process: 100 c.c. urine are exactly neutralized with decinormal ($\frac{N}{10}$) soda or potash, as for the estimation of free acid; it is then put into a flask capable of holding five or six times the quantity, 10 c.c. of normal alkali added, and the whole brought to boiling, taking care that the bladders of froth which at first form do not boil over. After a few minutes these subside, and the boiling proceeds quietly. When all ammoniacal fumes are

dissipated, the lamp is removed, and the flask allowed to cool slightly; the contents are then emptied into a tall beaker, and normal acid delivered from the burette with constant stirring, until a fine glass rod or small feather dipped in the mixture, and brought in contact with violet litmus-paper, produces neither a blue nor a red spot. The number of c.c. of normal acid is deducted from the 10 c.c. of alkali, and the rest calculated as ammonia; 1 c.c. of alkali = 0.017 gramme of ammonia. Example: 100 c.c. of urine were taken, and required 7 c.c. of $\frac{N}{10}$ alkali to saturate its free acid; 10 c.c. of normal alkali were then added, and the mixture boiled until a piece of moistened red litmus-paper was not turned blue when held in the steam; 4.5 c.c. of normal acid were afterwards required to saturate the free alkali; the quantity of ammonia was, therefore, equal to 5.5 c.c., which, multiplied by 0.017, gave 0.0935 gramme in 1,000 of urine.

Sulphuretted Hydrogen.—The urine may contain sulphuretted hydrogen after the inspiration of this gas or after the ingestion of sulphur. Its presence is demonstrated by acetate of lead.

Organized Substances.

BLOOD CORPUSCLES (HÆMOGLOBINE).

Blood elements are found in the urine under two forms:

(a) **As Hæmaturia**, in which the urine contains blood corpuscles, which impart to it an intensity of colour corresponding to their quantity.

(b) **As Hæmoglobinuria**, in which the urine contains the colouring principle of the blood, and few or no blood corpuscles.

Hæmaturia.—In this case the urine is of the colour of blood, or of a light brownish colour. It is opaque, and on standing deposits a grayish-red or grayish-brown sediment.

Heller's Reaction.—To a few c.c. of urine containing blood, add a little caustic soda, so as to render the liquid strongly alkaline. Heat to boiling. If blood be present, a bottle-green colour results, and the phosphates are precipitated in fine flakes containing the colouring matter of the blood, of a brownish-red colour.

Guaiacum Reaction.—Mix carefully 1 e.e. of tincture of guaiacum with an equal quantity of oxidized turpentine

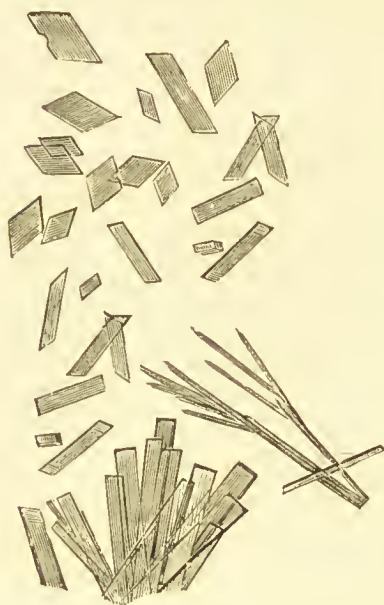


FIG. 49.—CRYSTALS OF HÆMO-
GLOBINE.

(‘Sanitas’). Drop gently from a tube along the wall of the vessel containing the urine. A part of the resin of the guaiacum separates rapidly under the form of a whitish precipitate, which becomes of a greenish colour; but if the urine contains the smallest trace of blood there forms below the resin an indigo-blue coloured zone, which on agitation gives a clear blue emulsion. Or add a few drops of tincture of guaiacum to the urine, and then an excess of ozonic ether—that is, a mixture of peroxide of hydrogen and ether. Shake the mixture: the

ether separates, and if blood be present, a fine sapphire-blue

colour results. As other substances besides hæmoglobine reduce the guaiacum, this test can be regarded only as corroborative.

Hæmin Reaction.—For this reaction the coagulum which is

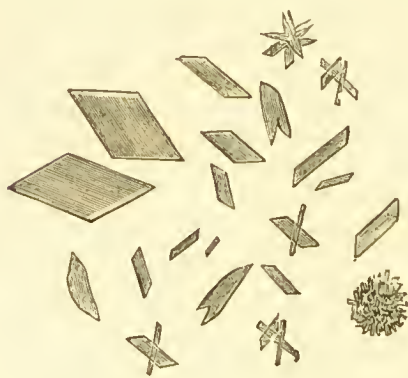


FIG. 50.—CRYSTALS OF HÆMIN.

deposited from the urine is to be gently heated to dryness with a fragment of chloride of sodium. Treat the mixture with two or three drops of glacial acetic acid. Heat on a glass slide. On cooling, characteristic crystals of hæmin are found. These are small rhomboidal tablets of a reddish-brown colour.

Lechine's Reaction.—Add one drop of acetic acid to 10 c.c.



PLATE II.



FIG. 1.—RED BLOOD-GLOBULES PRESENTING DIFFERENT DEGREES OF ALTERATION.

FIG. 2.—RED BLOOD-GLOBULES PRESENTING A RARER FORM OF ALTERATION, HIGHLY MAGNIFIED.

FIG. 3.—LEUCOCYTES—GRANULAR AND GRANULO-FATTY CHANGES.

FIG. 4.—MUCOUS CAST WITH ALTERED WHITE GLOBULES.

FIG. 5.—LINING OF STRAIGHT TUBE, ALMOST NORMAL.

[To face page 205.]

of urine, and agitate with 3 c.c. of chloroform. After a few minutes' repose the chloroform becomes red, if the urine contain the colouring-matter of the blood.*

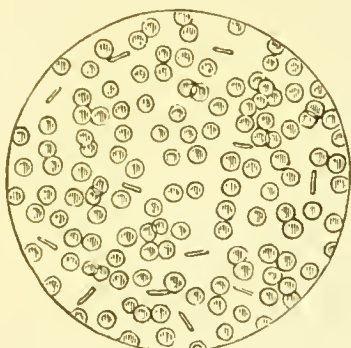


FIG. 51.—RED BLOOD GLOBULES.

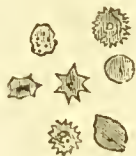


FIG. 52.—RED GLOBULES ALTERED IN THE URINE.



FIG. 53.—RED BLOOD GLOBULES DECOLORIZED IN THE URINE, WITH DOUBLE CONTOUR.

Microscopic Examination shows the blood-globules under the form of small discoidal corpuscles of a yellowish colour, slightly biconcave, with well-defined borders. In urine which has become alkaline, however, and in which the corpuscles have lain for a considerable time, the globules become swollen, and present serrated edges. Sometimes they present a double contour, and then become discoloured by the solution of the hæmoglobine in the alkali.

Hæmorrhagic cylinders are frequently met with in the urine, and possess an important diagnostic significance in relation to renal hæmorrhage. Rarely crystals of hæmatoidine are found in the urine.

Pathological Significance.—To determine whether the blood be from the bladder or kidney, several points have to be considered. When at the commencement of micturition the urine does not contain blood, or only a minute quantity, and the maximum of blood colour appears in the last drops of urine; when the colour of the urine is reddish, the reaction alkaline (ammoniacal), and the proportion of albumen is rela-

* *Pharm. Zeitung*, 1887.

tively feeble, there is reason to suppose that the hæmorrhage is of vesical origin. Even isolated, each of these symptoms would point to this conclusion.

Renal Hæmorrhage, apart from traumatic lesions and cancer, is usually moderate. The colour of the urine is grayish-brown or reddish-brown. The mixture of the blood with the urine is intimate, the reaction is acid, and the amount of albumen relatively abundant. Elongated or vermiform coagula of from 5 to 10 c.c. in length frequently form in the ureters. They are whitish in appearance, sometimes of the size of a quill. They are most frequently found in cases of renal hæmorrhage. Hæmorrhagic cylinders can form only in the kidney.

Spectrum Analysis.—Oxyhæmoglobine presents two well-marked absorption bands between the D and E Fraunhofer lines (in the yellow and green). Methæmoglobine, a modification of hæmoglobine containing as much oxygen as oxyhæmoglobine, presents a characteristic ray in the red. According to Hoppe-Seyler, urine in the fresh state never, or only very

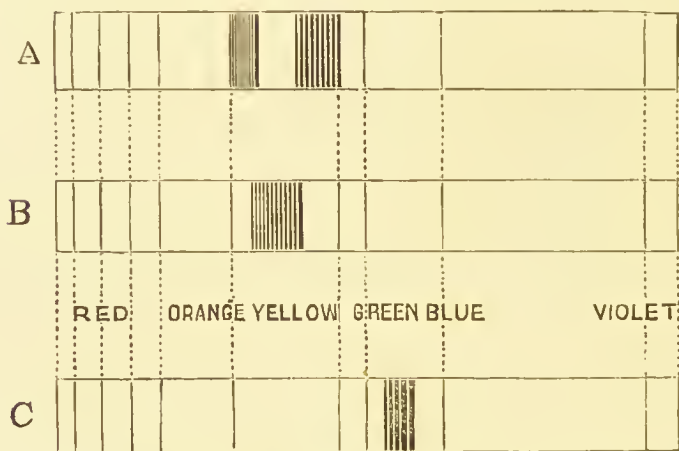


FIG. 54.—(a) Spectrum of Hæmoglobine ; (b) Spectrum of Reduced Hæmoglobine ; (c) Spectrum of Urobiline.

exceptionally, contains oxyhæmoglobine, but always methæmoglobine. Putrefaction reduces methæmoglobine to hæmoglobine, which by agitation with air produces oxyhæmoglobine. Fresh

urines, then, give the spectrum of methæmoglobine; if long kept, the spectrum of hæmoglobine or oxyhæmoglobine.

Hæmoglobinuria.—Hæmoglobinuria is symptomatic of exanthematous fevers, certain cases of poisoning, and nervous maladies, etc. The colour of the urine varies from ruby red to black. In typical cases the urine is clear, transparent, and approaches the colour of port-wine. Notwithstanding that chemical tests demonstrate the presence of the colouring matter of the blood, microscopic examination does not reveal blood

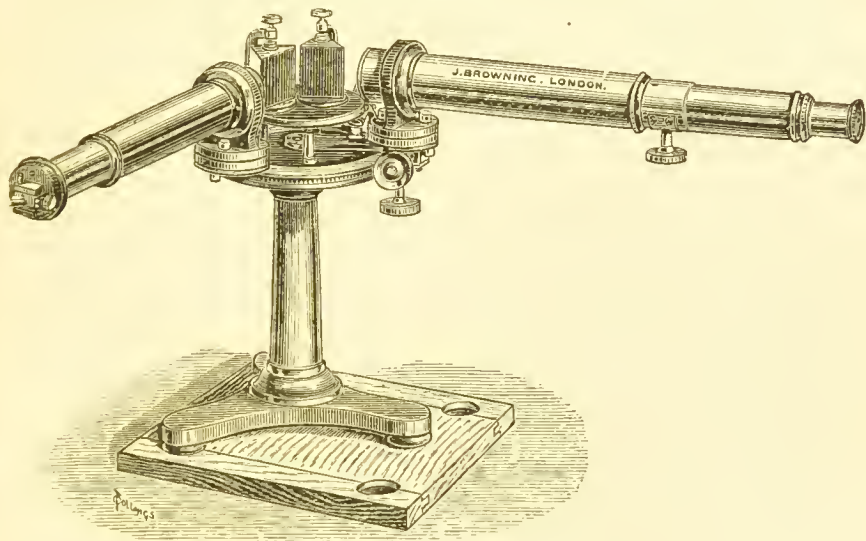


FIG. 55.—THE SPECTROSCOPE.

corpuscles. Frequently hyaline and granular casts are found, with a brownish detritus. From the chemical point of view the reactions of such urine are simply those of a solution of hæmoglobine. Heated to boiling, an albumen coagulum results, but this albumen is not coagulated as ordinary serum albumen in flakes which settle, but immediately forms a brownish coherent coagulum, which floats upon the surface, and can be lifted therefrom, and decolorized with boiling alcohol and sulphuric acid.

LEUCOCYTES (Pus).

Pus is found in the urine in cases of inflammation of some portion of the genito-urinary tract. When the amount is con-

siderable, and the evacuation is accomplished in a brief space of time, the existence of an abscess may be inferred, either in the kidney or in the cellular tissue of some of the organs adjacent to the pelvis. In the female the urine may contain pus from the vagina or uterus. Urine containing pus is usually of a pale, grayish-yellow, dirty colour. It presents a more or less considerable grayish sediment, which on microscopical examination

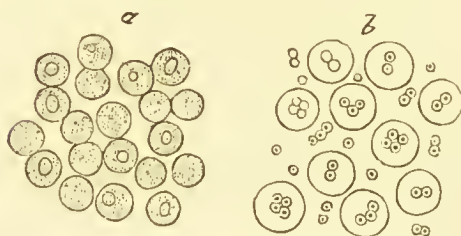


FIG. 56.—PUS CELLS.

(a) Normal ; (b) Acted on by Acetic Acid.

is found to consist of pus-cells, or leucocytes. These cells are round, often of crenated outline, have the same appearance as mucus-cells, are about twice the size of the red globules of the blood, and are entirely filled with granular contents. These granulations conceal the nucleus of the pus-cell (one or two). The addition of acetic acid dissolves the granulations, and the nuclei become apparent. Like the blood, pus is formed of two parts—one liquid, or plasma; the other solid, composed of the opaque whitish globules just mentioned. The plasma of pus may be separated by filtration. It is an amber-coloured, clear, alkaline liquid, coagulable by heat. It contains the following albuminoid compounds, viz., *globuline*, *serine*, *myosine*, and *pyine*. The last is precipitated by acetic acid as mucine is; but the precipitate is soluble in water, a circumstance which distinguishes it from mucine. Purulent urine is most frequently ammoniacal, and its sediment forms a viscous filamentous mass. Sometimes it is entirely transparent, and then all its parts adhere so intimately that it may be emptied from the containing vessel as a coherent gelatinous mass. Sometimes, under the action of carbonate of ammonia, the cells undergo certain important modifications. They become clear, their contour fades, and the nuclei are distinguished with difficulty. In such specimens of urine there are usually found numerous crystals of ammonio-phosphate of magnesia (triple phosphate) and of urate of ammonia. If a concentrated solution of potash be added to

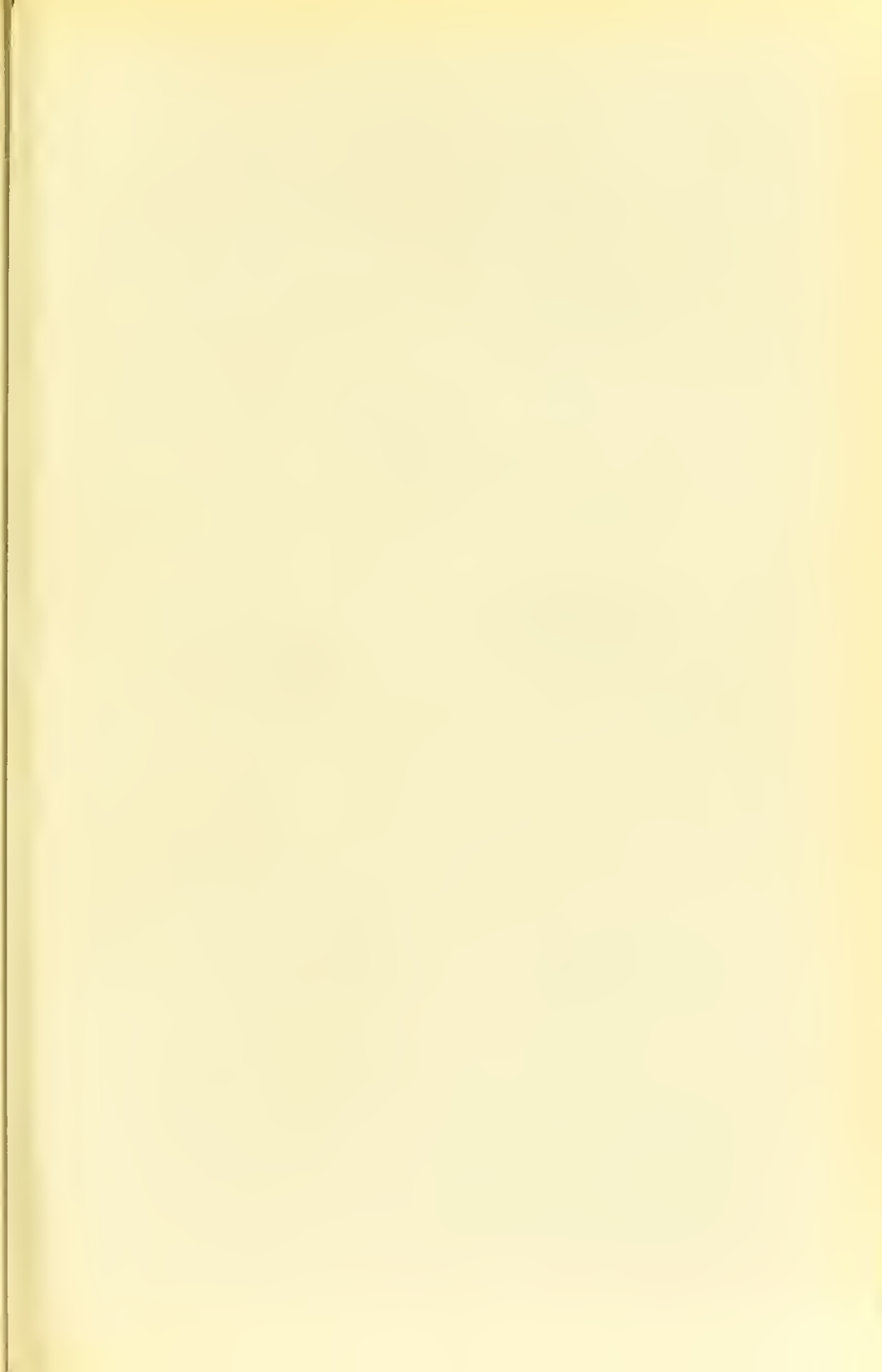


PLATE III.

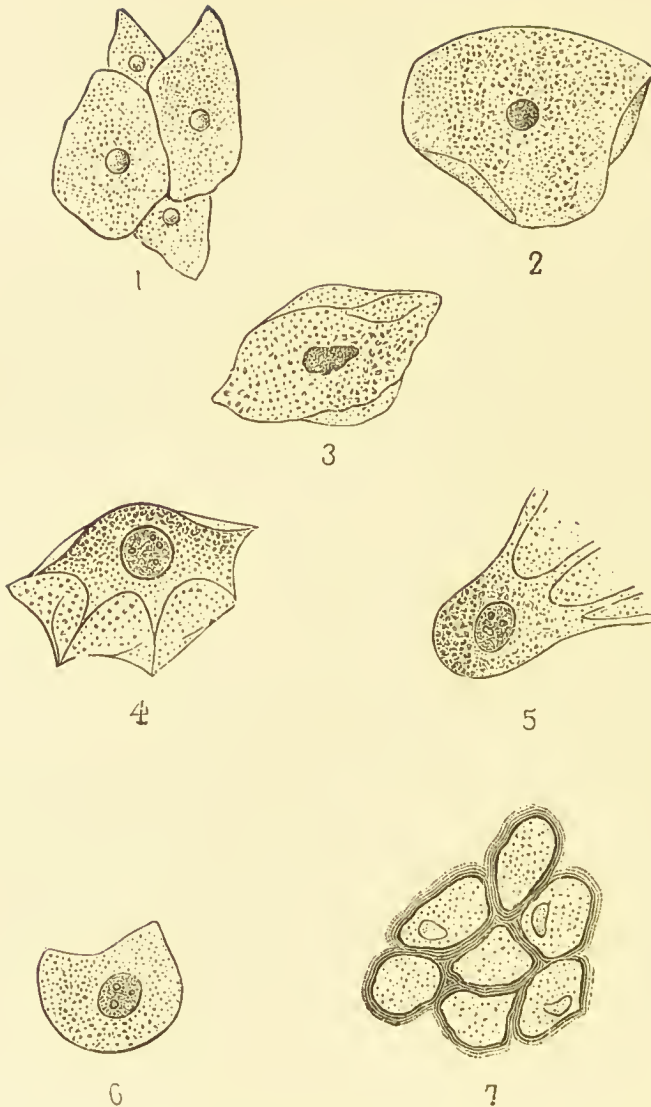


FIG. 1.—OVERLAPPING EPITHELIAL CELLS FROM THE VAGINA.
 FIG. 2.—VAGINAL EPITHELIAL CELL WITH FOLDED EDGES.
 FIG. 3.—ALTERED VAGINAL CELL (THE NUCLEUS DEFORMED).
 FIGS. 4 AND 5.—NORMAL BLADDER CELLS OF THE RABBIT (SUPERFICIAL LAYER).
 FIG. 6.—NORMAL CELL FROM RABBIT, MIDDLE LAYER.
 FIG. 7.—BLADDER EPITHELIAL CELLS AS APPEARING IN URINE AFTER TWENTY-FOUR HOURS.

urine containing pus, a gelatinous coagulum results; while in the case of mucus it is liquefied and dissolved under like circumstances. In certain cases of gonorrhœa pus filaments may be found. Urine containing pus is necessarily coagulated by heat, and by filtration the pus globules and the albumen may be separated. Sediments of earthy phosphates which present a certain similarity to pus may be distinguished from it by their solubility in acetic acid.

Day's Test for Pus.—The late Dr. Day, of Geelong, recommended the following test for pus. To the purulent urine add a drop or two of tincture of guaiacum, when a clear blue colour is produced. If the pus be dry, before applying this test it is necessary to moisten it with water. Recently oxygenated water has been recommended as a test. It determines an effervescence due to oxygenation.

Mucus.

The appearance of mucus is usually characteristic. It forms a flocculent, cloudy, semi-transparent deposit of feeble coherency. Owing to its feeble density, it remains long suspended in the urine. It becomes fluid on the addition of ammonia, whereas pus becomes gelatinous. Urine containing mucus does not necessarily give an albumen precipitate. Day's test for mucus consists in the application, first, of oxidized tincture of guaiacum, which alone undergoes no change in contact with mucus, but on the addition of carbolic acid or creosote the colour of the guaiacum becomes bright blue. On microscopic examination mucus is found to consist principally of filaments, made more manifest by the addition of acetic acid, and some clear, round cells. Whenever the addition of acetic acid to urine causes a slight cloudiness, the urine contains mucus. If microscopic examination reveals leucocytes, and if albumen exist, there is *muco-pus* in the urine.

EPITHELIAL CELLS.

In the cloudy deposit which forms in normal urine most frequently exist epithelial cells from the bladder. The desquamation of epithelium may take place from the kidney to the urethra, and the origin of the cells is determined by their special

character. The epithelial covering of the genito-urinary tract comprises three layers: the superior layer, formed of large rounded or polygonal scales, with a nucleus; the middle layer, composed of spindle cells, whose tapered extremity is insinuated into the inferior layer; and the innermost layer, composed of ovoid elongated cells, smaller than those of the surface. Desquamation of the superficial cells is constantly taking place. The epithelial cells most frequently found are those of the bladder. They appear as transparent rectangular plaques, with rounded or elliptic angles, with a nucleus with a border more defined than that of the cells of the vagina. They are isolated, or aggregated together in plaques, of greater or less size. By their borders they are in apposition to one another, and sometimes they are slightly imbricated. These cells are found in the urine of females as well as of men. In the former case vaginal epithelium may be found. These are abundant when the vagina is the seat of inflammation. They are of the same form as the cells of the bladder, but are larger, with thinner edges and a smaller central nucleus. These cells resemble those of the inferior portion of the ureter and prepuce.

The cells of the neck of the bladder are caudate. They probably represent the middle layer of the epithelial covering. The cells of the ureters and pelvis of the kidney are smaller than the preceding, and are club-form, having a nucleus in the head, or enlarged portion.

The epithelium of the ureter is stratified pavement. The cells are long and cylindric. They are granular, and above the oval nucleus there is found one, rarely two, brilliant drops, which resist the action of acetic acid.

The cells which come from the pelvis of the kidney are frequently small, round, or oval, with large nuclei, and are generally united in plaques. This grouping is very significant, for if along with it there is acidity of the urine, we have here a pathognomonic distinction between pyelitis and cystitis. Renal epithelium is formed of round or polyhedral cells, generally isolated, and with a granular or clear protoplasm, granular in the cells of the *tubuli contorti*, clear in those of the descending branch of the loop of Henle. The nucleus is large and distinct.

PLATE IV.

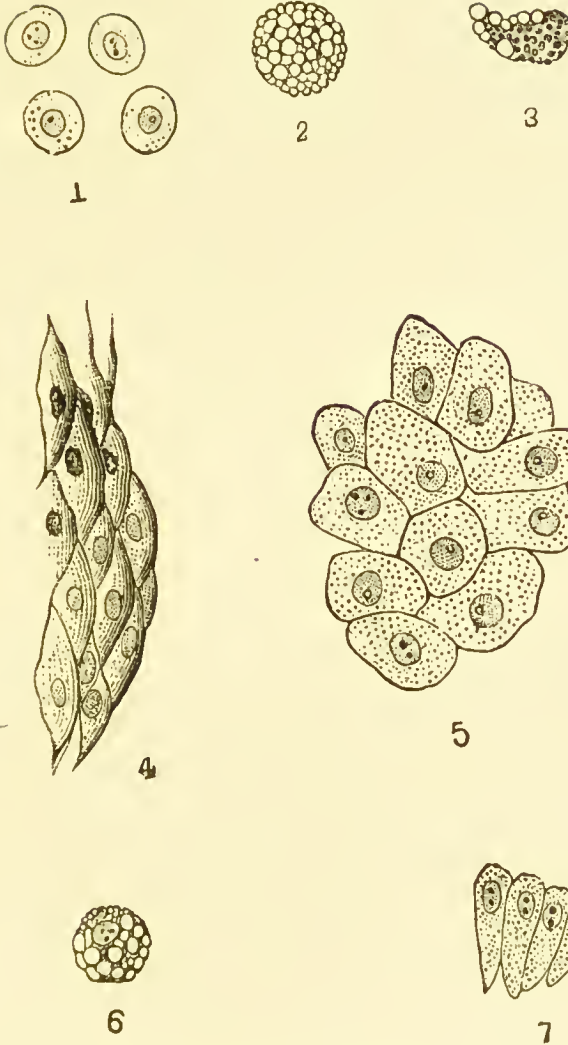


FIG. 1.—CELLS FROM THE STRAIGHT TUBES.

FIG. 2.—FATTY DEBRIS, WITHOUT NUCLEUS, FROM THE CONVOLUTED TUBES.

FIG. 3.—IRREGULAR FATTY MASS FROM THE SAME REGION.

FIG. 4.—OVERLAPPING EPITHELIAL CELLS FROM THE VAGINA.

FIG. 5.—NORMAL CELLS FROM MIDDLE LAYER OF THE BLADDER.

FIG. 6.—NUCLEATED FATTY MASS FROM THE CONVOLUTED TUBES.

FIG. 7.—NORMAL CELLS FROM THE DEEP LAYER OF THE BLADDER AND URETER.



These cells undergo great modifications as the result of pathological processes. Thus, in cases of fatty degeneration of the kidney they contain small refractive fatty granulations, and their volume is much augmented. They are easily recognised. When they are found on tube-casts, or when united with other elements, they constitute *epithelial casts*.

The epithelial cells of the urethra are elongated, cylindrical, and slender inferiorly. They are granular, and possess an oval nucleus.

The presence of epithelial cells in the urine is of no pathological importance when in small quantity. If abundant, they indicate a corresponding amount of desquamation, and consequently inflammation of some portion of the genito-urinary tract. The form of the cell may indicate the seat of the disease. Abundant desquamation is almost invariably associated with the formation of pus, and leucocytes and albumen are then found in the urine. This applies more especially to cystitis, for in nephritis tube-casts take the place of epithelial cells.

SPERMATOOA.

Spermatozoa are found in the urine after coitus, after involuntary seminal emission; usually in cases of spermatorrhœa; after epileptic attacks; may be passed from the urethra at stool, especially when the bowels are constipated, and when the prostatic ducts are relaxed and atonic; in cases of chronic prostatitis, and during the course of several constitutional diseases, such as typhoid fever, and after apoplectic and epileptic attacks.* Like pus, the semen is composed of a fluid and a solid portion. Urine containing semen is not usually markedly cloudy. The liquid portion contains an albuminous principle, *spermatine*, which is precipitated by acetic acid, and soluble in an excess, by which it is differentiated from *mucine*. Allowed to stand, however, for

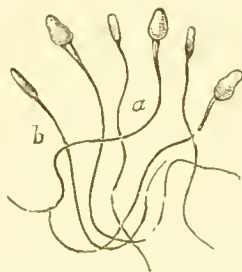


FIG. 57.--(a) (b) SPERMATOOA LARGELY MAGNIFIED.

* Vide 'Prostatorrhœa,' by Author (*Lancet*, October, 1882), and 'The Functional Diseases of the Urinary and Reproductive Organs,' second edition (Churchills, London).

some time in a conical glass, the semen deposits in from six to eight hours, when it may be examined microscopically, and the characteristic appearance of the spermatozoa be demonstrated. Spermatozoa resemble the tadpole in form, composed as they are of a head, which is ovoid or triangular, and a long filiform tail. In semen recently ejaculated the spermatozoa exhibit great activity. Sometimes spermatozoa



FIG. 58.—SPERMATOZOA, WITH ACID URATE OF AMMONIA, BLADDER EPITHELIUM, AND FRAGMENTS OF PROSTATIC CASTS (PASSED AT STOOL).



FIG. 59.—SPERMATOZOA, BLADDER EPITHELIUM, AND PROSTATIC CASTS (PASSED FROM URETHRA AT STOOL).

are found in fragments in the urine, the tail especially being broken; notwithstanding this, the head can be easily recognised. In the case of copious seminal losses, besides the spermatozoa, certain particles like sago grains (corpuscles of Lallemand-Trousseau) are found in the urine. According to Furbringer, they are composed of a substance analogous to globuline, and come from the seminal vesicles. In the absence of spermatozoa these bodies do not possess any diagnostic significance. If semen be allowed to dry on a glass slide, prismatic or pyramidal colourless or yellow crystals, grouped in a stellar form, are observed (crystals of Böttcher). According to Schreiner, these



PLATE V.

Fig 2

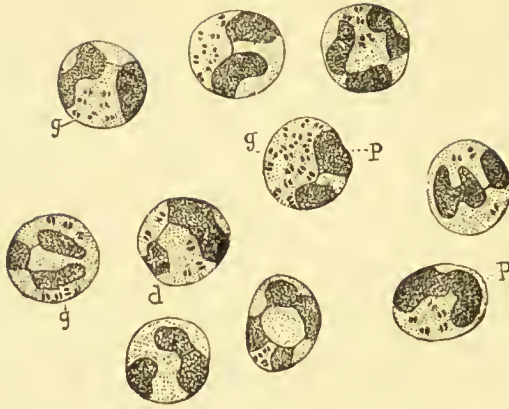


Fig1



Fig3

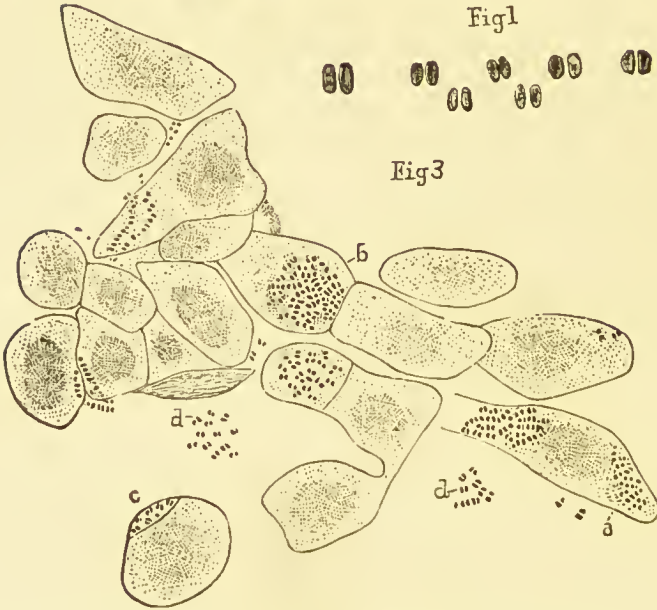


FIG. 1.—GONOCOCCI ENLARGED ABOUT 200 DIAMETERS.

FIG. 2.—GONOCOCCI IN PUS CELLS. (*d*) Pus cell. (*p*) Cell protoplasm contracted by alcohol. (*g*) Gonococci (12 immer. objective).

FIG. 3.—ISOLATED GONOCOCCI IN EPITHELIAL CELLS. (*a*) Cell containing at each extremity a mass of gonococci. (*b*) A mass of gonococci upon an epithelial cell. (*c*) Cell with a few gonococci. (*d*) Gonococci outside the cell.

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crystals are a combination of phosphoric acid with an organic substance.

Spermatic sediments frequently contain crystals of oxalate of lime, especially in cases of spermatorrhœa, leucocytes, epithelial cells, granules of urates, crystals of uric acid and of triple phosphate.

ORGANISMS FOUND IN URINE.

The parasitic animal most frequently found in the urine, in Europe, is *Echinococcus hominis*. It is either found in suspension in the urine or in its sediments. It is easily distinguished by its hooklets and stratified membranous scales.

In hot countries, and notably in Egypt and South Africa, the urine is often found to contain the egg and ciliated embryos of the *Distoma hæmatobium* or *Bilharzia hæmatobia*. This worm is also found in the *vena portæ* and its branches, as well as in the venous plexus of the bladder. The eggs are deposited in great number by the female in the interior of the vessels, and within the vesical mucous membrane, and ultimately perforate the membrane, hæmaturia being the result. In this case the urine is bloody, and deposits a reddish flocculent sediment, containing blood-crystals, leucocytes, and eggs of the *Distoma*. In the East Indies there is found in the urine and in the blood of persons suffering from chyluria, embryos of the *Filaria sanguinis hominis*, which have also been observed by Brésil in endemic hæmaturia, this affection being due to their existence in the blood. Almost invariably chyluria is accompanied by hæmaturia (hæmato-chyluria). The so-called *bacillus of tuberculosis* is stated to be found in the urine of persons suffering from phthisis. It is thus held to constitute a valuable differentiating feature between typhoid fever and miliary tuberculosis of the genito-urinary system. Sometimes there is accidentally found in the urine *Trichomonas vaginalis*, a parasite living in the vaginal mucus; the *Bodo* or *Cercomonas urinarius* described by Hassall in alkaline urine; the *Oxyuris vermicularis*, whose habitat is the inferior portion of the intestine; the *Strongylus gigas* from the kidney; the *Ascaridis lumbricoides* and its eggs, passing through an abnormal communication from the intestine

to the bladder. Of *Saccharomycetes*, the *Saccharomyces urine*, which is probably identical with the yeast fungus, *Saccharomyces cerevisiæ*, has been found in diabetic urine. These cells are ovoid, and brilliant, and of about the size of a red blood-corpuscle. *Sarcinæ* may also be found in the urine, independently of their existence in the stomach.

According to Pasteur, Tieghem, and Miguel, the *Micrococcus* and *Bacillus urine*, which are the cause of the decomposition of urea, may also be found in the urine.

In acute infectious maladies, such as diphtheria, typhoid fever, scarlet-fever, small-pox, etc., a large quantity of bacteria are often found in the urine, almost invariably with the presence of albumen. In cases of gonorrhœa the *Gonococcus* of *Neisser* often exists in the urine. This element is by no means pathognomonic of gonorrhœa, as many cases of gonorrhœa have been observed where it was absent. This microphyte is found in the purulent deposit in the form of small round or oval grains, most frequently aggregated in groups. They are readily stained with methylene blue and fuchsine.

PLATE VI.

Fig 1

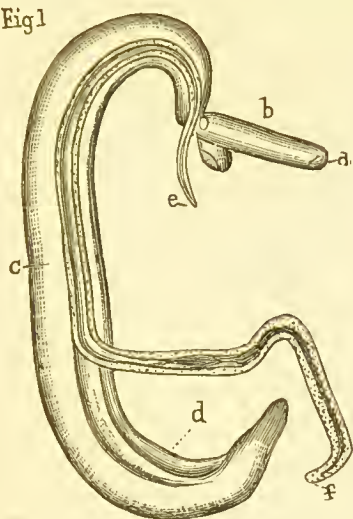


Fig 2

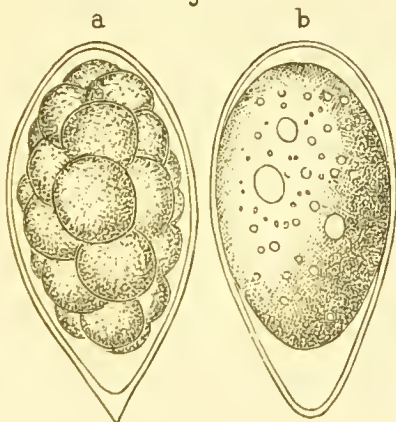


Fig 3



FIG. 1.—*BILHARZIA HÆMATOBIA*. The inferior extremity of the female protrudes from the gynæcophoric canal of the male. (*b*, *c*, *d*) Male. (*a*) Mouth-sucker. (*e*, *f*) Female in part free.

FIG. 2.—Two EGGS OF *BILHARZIA HÆMATOBIA*. (*a*) With large segmentation of the vitellus. (*b*) With vitelline granulations.

FIG. 3.—(*a*, *b*, *c*) Embryos of filaria. (*a*) Head. (*b*) Tail. (*c*) Body (*d*) Egg containing an embryo. (*e*) Egg showing vitelline segmentation.

[To face page 214.



PLATE VII.

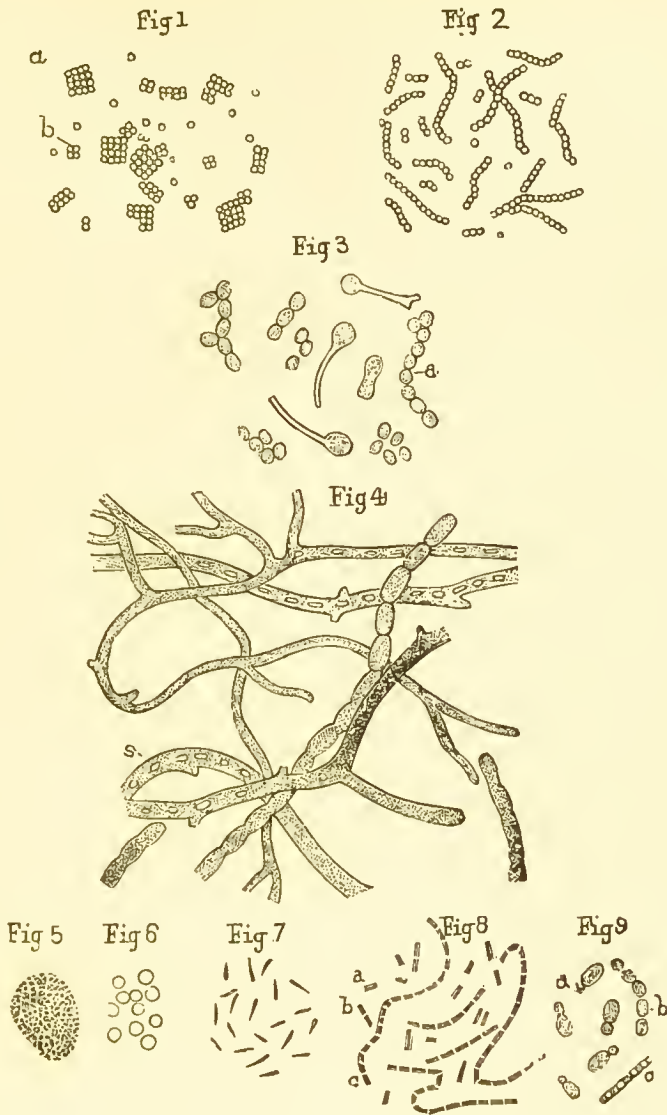


FIG. 1.—*SARCINÆ URINÆ*. (a) Group of sixteen. (b) Group of four.

FIG. 2.—*MICROCOCCLUS URINÆ*.

FIG. 3.—FERMENT OF SACCHARINE URINE. (a) Cells in opposition to each other.

FIG. 4.—*PENICILLIUM*. (s) Spore in mycellium tube.

FIG. 5.—MASS OF *MICROCOCCLUS* IN ALBUMINOUS URINE.

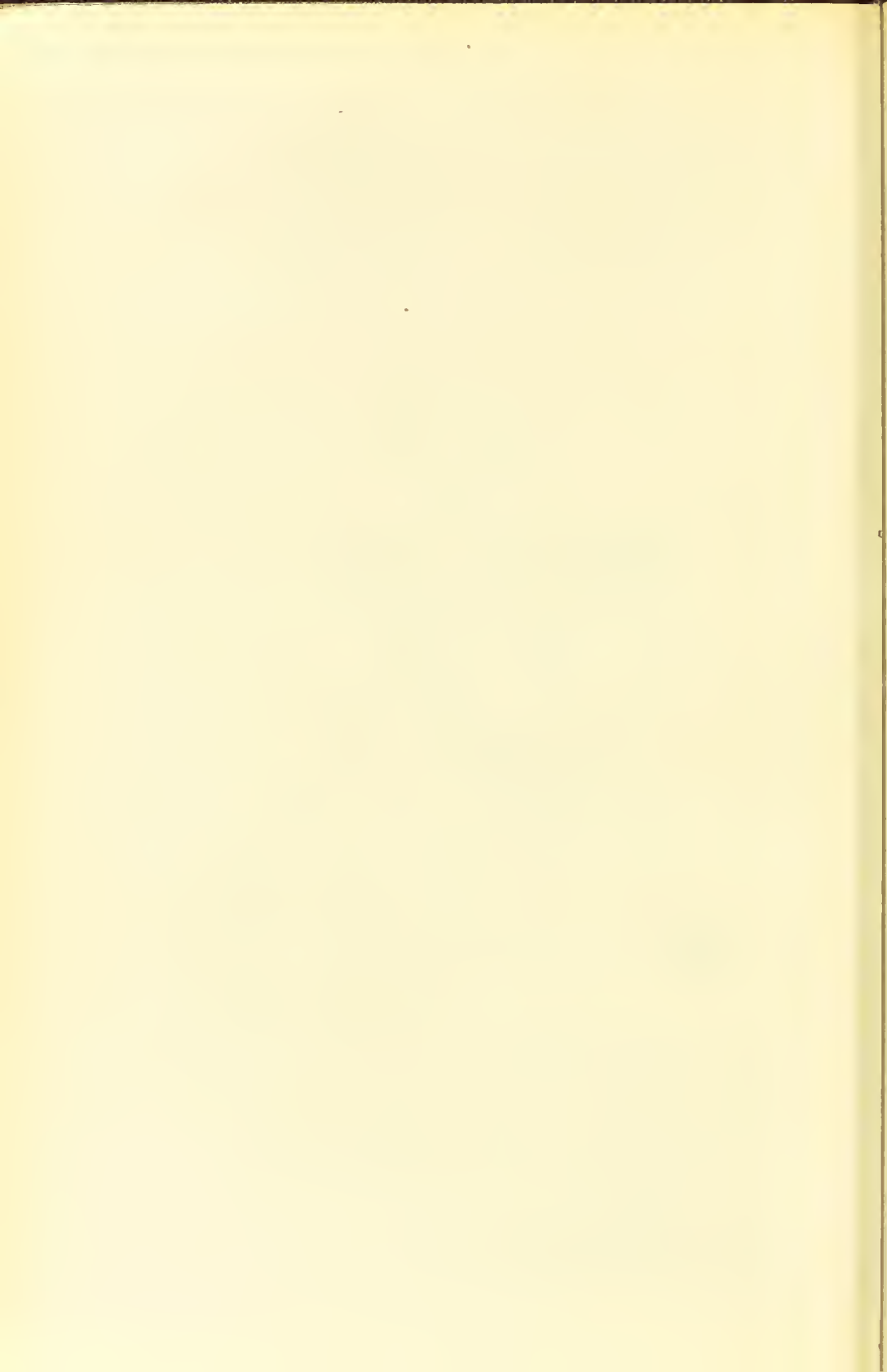
FIG. 6.—YEAST CELLS.

FIG. 7.—*VIBRIOS*.

FIG. 8.—*BACILLI*. (a) Isolated bacillus. (b) Bacilli joined together. (c) Chain of bacilli.

FIG. 9.—YEAST CELLS. (a) Oval cells. (b) Cells joined together. (c) Bacteria.

[To follow Plate VI.]



CHAPTER VI.

SEDIMENTS.

UNDER ordinary conditions the normal and pathological elements which have engaged attention in the foregoing pages are found in a state of solution in the urine. When, however, there happens to be either relatively or absolutely an augmentation of those constituents in the urine, they may, in consequence, undergo precipitation, either in the urinary passages or in the urine after it is voided from the bladder and has become cold. In the former case the urine is more or less milky when passed, while in the latter it is limpid and transparent. In other cases the urinary sediment is due to hyperacidity of the urine, or, on the contrary, to an absence of the normal acidity. There are certain urinary constituents which continue in solution in normally acid urine, but which undergo precipitation when the urine becomes either preternaturally acid or unduly alkaline, and this change may take place either before or after the emission of the urine. Sometimes new insoluble combinations are formed. Sediments may thus be composed of bodies which on account of their insolubility are only found in suspension in the urine, these constituents being always of an organized pathological nature, and designated *organized sediments*, in contradistinction to the *non-organized* sediments, which may be composed either of mineral or organic substances.

Sediments may thus be frequently a combination of non-organized mineral bodies or of organized organic elements. When the sediments form in the urinary passages, and are detained there, they may become *concretions* of more or less

size. In small form they may be expelled with the urine as *gravel*; in larger size they may become *renal* or *vesical calculi*.

Examination of Sediments.—In order to determine the nature of urinary sediments, both microscopic and chemical examination are most frequently required. As a preliminary step, however, the sediment must be isolated. In order to accomplish this, the urine is decanted into a conical glass, and allowed to stand undisturbed until a deposit takes place. The clear, supernatant fluid is then poured off carefully, and a pipette introduced into the remaining portion. Holding the pipette in a vertical position, the deposit accumulates in its narrower portion, and it can now be transferred to an object-glass. Microscopic examination can then be made with a power varying from 200 to 400 diameters. A chemical examination may be made by allowing a drop or two of the reagent to penetrate between the slide and the cover-glass.

Non-Organized Sediments.—The non-organized sediments most frequently met with are uric acid and urates, oxalate of lime and earthy phosphates (phosphate of lime and triple phosphate); and more rarely xanthine, hippuric acid, tyrosine, bilirubine, indigotine, hæmatoidine, and carbonate and sulphate of lime.

Distinctive Characters.—The following table exhibits the differentiating features of the sediments of this group :

I. The Urine has an Acid Reaction.

A. *The Sediment is Amorphous.*

1. It is composed of small granules which dissolve on heating; acetic acid dissolves them, and after some hours small rhomboidal tables of uric acid separate (crystals of uric acid and of oxalate of lime may also be contained in the sediment).

The sediment is composed of urates (vide pp. 74 and 75).

2. The sediment presents the appearance of dumb-bell crystals, and is insoluble in concentrated acetic acid, but soluble in hydrochloric acid without separation of crystals.

The sediment consists of oxalate of lime (vide pp. 93 and 94).

3. The sediment is insoluble in acetic acid and concentrated hydrochloric acid.

It consists of sulphate of lime.

4. The sediment consists of round, refractive bodies of a pearly colour.

It consists of fat (vide p. 195).

5. The sediment consists of yellow granular masses.

It consists of bilirubine (vide p. 224).

B. The Sediment is Crystalline.

1. Yellow or brown crystals of rhomboidal form, isolated or grouped in diverse manners, alone or accompanied with urates and oxalate of lime, soluble in soda; and the addition of concentrated hydrochloric acid gives after the lapse of a few hours small yellow rhomboidal plates.

Uric acid (vide p. 70).

2. Colourless octahedral crystals, yellow in the case of urine containing bile, transparent, very refractive, envelope form, sometimes of quadrangular prismatic forms, terminated by pyramids, insoluble in acetic acid, but soluble in hydrochloric acid.

Oxalate of lime (vide p. 93).

3. Large crystals of the coffin-lid shape, in urine faintly acid, in appearance somewhat similar to oxalate of lime crystals, but soluble in acetic acid.

Triple phosphates (vide pp. 222, 223).

4. Small tubular crystals, regular and six sided, insoluble in acetic acid, but soluble in ammonia.

Cystine (vide pp. 108 and 109).

5. Colourless needle-shaped crystals, insoluble in acetic acid and soluble in ammonia. The addition of hydrochloric acid causes the deposition of small hexagonal plates.

Xanthine (vide p. 224).

6. Large rhombic crystals, strongly refractive, elongated, and very fine. Their angles are rendered opaque and destroyed by carbonate of ammonia; frequently found in alkaline urine.

Basic phosphate of magnesia (vide p. 114).

7. Isolated or grouped prisms. (a) Soluble in ammonia.

Hippuric acid (vide p. 83).

(b) Insoluble in ammonia and acids.

Sulphate of lime.

8. Cuneiform prisms terminating in points, isolated or grouped together in stellar form; soluble in acetic acid and segregating in ammonia.

Neutral phosphate of lime.

9. Tufts of fine needle-like crystals, insoluble in acetic acid, and soluble in ammonia and hydrochloric acid.

Tyrosine (vide p. 224).

10. Small rhomboidal tables of a yellow colour, and accompanied by amorphous granular masses of a similar colour, soluble in soda; and on contact with acetic acid they surround themselves with a multicoloured areola, in which a green zone is observed.

Bilirubine (vide p. 224).

11. Needle-formed crystals, sometimes rhombic, and yellow or brownish-yellow, becoming blue in contact with nitric acid.

Hæmatoidine.

II. The Urine has an Alkaline Reaction.

If the urine becomes alkaline only after emission, it may contain such sediments as uric acid, oxalate of lime, sulphate of lime, etc. If the urine, on the other hand, is eliminated with an alkaline reaction, or if it deposits a sediment while it is becoming alkaline, the following sediments may be found:

A. The Sediment is Amorphous.

1. It is composed of small granules soluble in acetic acid:

(a) Without evolving gases—*Earthy phosphates.*

b) Evolving bubbles of gas—*Carbonate of lime.*

2. Masses in form of dumb-bells, soluble in acetic acid, with disengagement of gas bubbles.

Carbonate of lime.

3. Spheroidal masses of a dark colour, with crystalline points, soluble in hydrochloric and acetic acids, with subsequent deposition of rhomboidal tables of uric acid.

Urate of ammonia (vide p. 75).

B. The Sediment is Crystalline.

1. Large colourless prisms of coffin-lid shape, very soluble in acetic acid.

Ammonio-phosphate of magnesia (vide p. 109).

2. Masses of blue needle-formed crystals, and small tabular blue crystals.

Uroglauceine or indigotine.

Uric Acid and Urates.—Sediments of urates are most frequently observed in acute febrile affections, such as in acute rheumatism, pneumonia, etc., or during exacerbations of chronic affections, especially in disorders of the digestive apparatus, such as dyspepsia and chronic gastric catarrh; and in affections of the respiratory passages, such as dyspnoea, asthma, pulmonary emphysema, etc. The formation of urates in the urine is not always necessarily due to the excess of uric acid in the urine. In cases of rheumatism, for example, urates are found in abundance in the urine, while the amount of uric acid is usually normal. It is to the presence of acid phosphates in the urine that the precipitation of urates is most frequently to be ascribed, the neutral urates being thus transformed into acid salts, which are much less soluble; or otherwise, the volume of urine eliminated being diminished, there is not a sufficiency of water to hold the urates in solution. Cooling of the urine also causes a precipitation of the urates, as they are much more soluble in hot than in cold solutions. Hence deposits of urates may be found in the urine of perfectly healthy individuals, especially after violent physical exertion, large ingestion of food, after abundant sweatings, and during winter, the urine being exposed to a low temperature. Cylindrical masses composed of urates are not infrequently observed in the urine of infants, these being of a brown or reddish colour, and originating in the renal tubes. The decomposition of neutral urates by acid phosphates, during the earlier stages of the decomposition of urine, causes a deposition of acid urates and uric acid (*vide* p. 220).

Sediments of free uric acid are of rarer occurrence! They are sometimes found alone, at other times accompanied by urates. In the former instance they are expelled with the urine in the form of *uric acid gravel*, in which case they originate in the urinary passages.

Characters of Urates.—Deposits of urates, as we have already seen, are of yellow or brick-red colour, according as urinary or hepatic pigments predominate. They usually consist of a mixture

of various urates, most frequently of potassium and sodium, sometimes urate of ammonia, and more rarely of urate of lime



FIG. 60.—URIC ACID.



FIG. 61.—URIC ACID.

and magnesia. Deposits of urates are not infrequently combined with free uric acid and oxalate of lime.

Examined microscopically, these deposits present the appearance of fine amorphous granulations irregularly grouped, and of

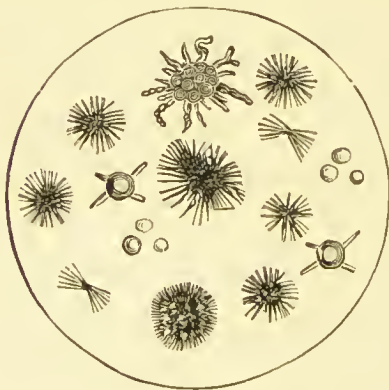


FIG. 62.—URATE OF SODIUM.

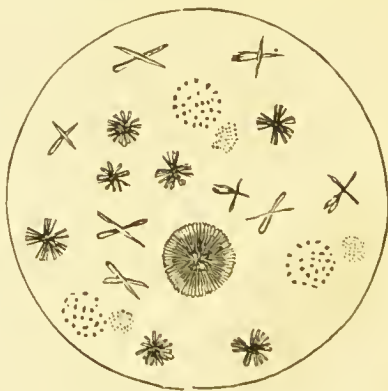


FIG. 63.—URATE OF AMMONIA.

easy solubility by heating, precipitating again when cooling takes place. Should the proportion of urates be so considerable as to

render obscure the presence of other sediments, such as uric acid and oxalate of lime, separation may be effected by filtering the heated urine : the urates will pass through, and the uric acid and the oxalate of lime will remain on the filter. Treated with hydrochloric acid, deposit of urates yields uric acid.

Urate of Ammonia.—

This urate is most frequently found in alkaline urine, in combination with earthy phosphates, and in the form of fine granulations.

Uric Acid Sediments present the form and characteristics already described (*vide* p. 70).

Hippuric Acid.—Sediments of hippuric acid are rare (*vide*, p. 83 *et seq.*). Hippuric acid crystals resemble in appearance certain forms of uric acid and of triple-phosphate. They are distinguished from the former by not giving the murexide reaction, and from the latter by their insolubility in hydrochloric acid.

Oxalate of Lime.—

Occasionally, in perfect health, oxalate of lime may be found in the urine. It may exist as a sediment, or be suspended in the mucus of the urine. It exists in considerable abundance in the urine in certain diseases, in connection with the *oxalic acid diathesis*, and after the ingestion of certain vegetables.

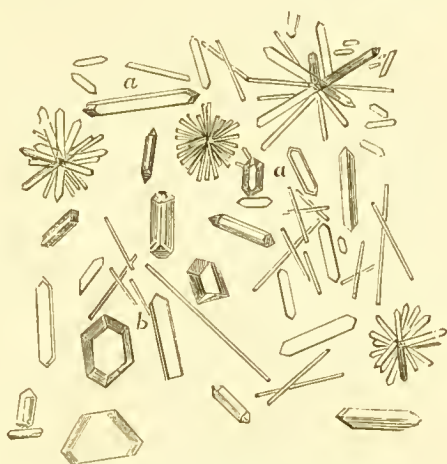


FIG. 64.—HIPPURIC ACID.
(a) Rhombic prisms ; (b) needle form.

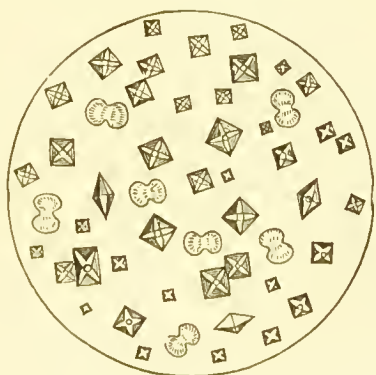


FIG. 65.—OXALATE OF LIME.

Oxalate of lime precipitates from the urine simultaneously with acid urates and uric acid.

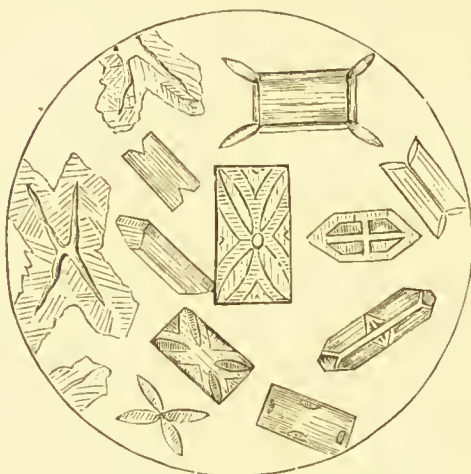


FIG. 66.—TRIPLE PHOSPHATES (PHOSPHATES OF AMMONIA AND MAGNESIA).

rickets, *mollities ossium*, etc. These phosphates are deposited from the urine in consequence of its becoming neutral or alkaline, and being thus incapable of holding the earthy phosphates in solution.

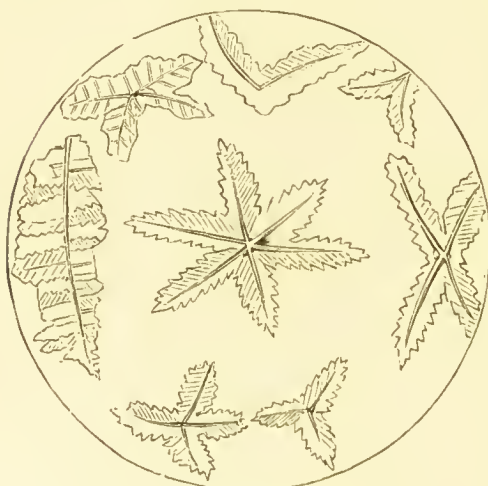


FIG. 67.—TRIPLE PHOSPHATES (FEATHERY FORM).

Earthy Phosphates.—The triple-phosphate presents the above appearance (Fig. 66). The crystals are of considerable size, and

Sometimes the crystals of oxalate of lime resemble certain forms of chloride of sodium and triple phosphate. From the former they are distinguished by their insolubility in water, and from the latter by their insolubility in acetic acid.

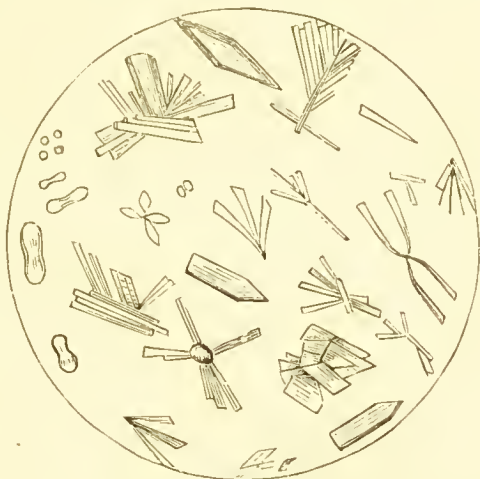
Earthy Phosphates.

—Sediments of earthy phosphates are usually found in chronic diseases, such as phthisis, rickets, *mollities ossium*, etc. These phosphates are deposited from the urine in consequence of its becoming neutral or alkaline, and being thus incapable of holding the earthy phosphates in solution. If the urine contain a sediment of earthy phosphates when voided, it is evident that the sediment forms within the bladder, and is probably associated with some inflammatory condition of the genito-urinary tract. Long persistence of earthy phosphates in the urine would probably indicate vesical calculi.

Characters of

are very soluble in acetic acid. When the deposition of earthy phosphates is the result of rapid evaporation, the crystals present the "feathery" form (Fig. 67).

Phosphates of lime and magnesia deposit from urine which has become alkaline, or is voided as such. They present the form of amorphous, transparent, and rounded plaques, distinguishable from urates in not being dissolved by heating. These phosphates may exist alone, or be combined with ammonio-phosphate of magnesia. The deposit may be so thick as to be mistaken for pus.



Phosphate of Lime FIG. 68.—**STELLAR PHOSPHATES OF LIME.** is found in the urine in the form of prismatic crystals, colourless, and isolated or in tufts. It is distinguished from uric acid by its solubility in acetic acid.

Phosphate of magnesia is sometimes found in neutral or concentrated alkaline urines in the form of fine refractive rhomboids. When the urine is not coloured by pigments to an abnormal extent, the deposits of earthy phosphates present a white appearance. They are insoluble in water and in alkalies, but dissolve readily in mineral acids and acetic acid.

Carbonate of Lime.—Sometimes crystals of carbonate of lime are found mixed with the earthy phosphate deposits of the *dumb-bell* variety. They are distinguished from oxalate of lime crystals of like form by their easy solubility in acetic acid.

Sulphate of Lime.—In rare instances this salt is found in the urine under the form of colourless elongated needles or tubular crystals, insoluble in ammonia and acetic acid, and sparingly soluble in nitric and hydrochloric acids.

Cystine (*vide* p. 179).—Deposits of cystine are rare in the

urine. They may, however, persist a long time in the urine without any evident constitutional derangement.

Xanthine.—The presence of xanthine in the urine was first demonstrated by Bence Jones in a case of nephralgia. Xanthine crystals are of two forms (Fig. *a*, and the form *b*). The latter are produced when the xanthine is dissolved by heating (thus contra-distinguished from uric acid), treated with hydrochloric acid, and evaporated. These crystals are then deposited. They are soluble in water.

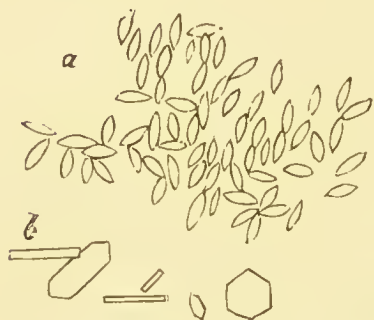


FIG. 69.—XANTHINE.

Tyrosine.—In cases of yellow atrophy of the liver tyrosine has been found as a urinary sediment.

Bilirubine.—In certain cases of jaundice and pyelitis, bilirubine has been found as a urinary deposit. It either presents in an amorphous form or its character-



FIG. 70.—TYROSINE.

istic crystalline form. It is of a yellow or brown colour, and is very soluble in alkalis and chloroform. With nitric acid it gives the special bile-pigments' reaction.

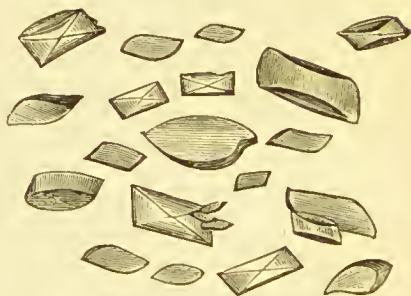


FIG. 71.—BILIRUBINE.

Uroglaucine, or Indigotine.—In urine containing a large amount of indican, uroglaucine, or indigotine, may be found as a deposit. It presents under the form of scales or needles of a bluish colour.

Hæmatoidine.—Ebstein and other observers have found hæmatoidine in certain urinary deposits, especially in cases of pyelitis in pregnancy, in amyloid degeneration of the kidneys, in scarlatinal nephritis, in typhoid fever, in cancer of the kidneys, and cancer of the bladder. Hæmatoidine is the product of decomposition of the blood, and is found in cases of blood extravasation of long standing. Microscopic examination shows it in the form of acicular, or sometimes rhomboidal, crystals (Fig. 72). These crystals are often found deposited on the surface of tube-casts, and bladder and renal epithelium. They are of a yellowish or reddish-brown colour, and are distinguished from bilirubine, with which they are apt to be confounded, by a transient blue colour which contact with nitric acid imparts to them.



FIG. 72.—CRYSTALS OF HEMATOIDINE.

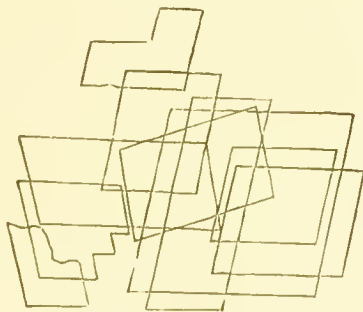


FIG. 73.

Cholesterine is sometimes found as a urinary deposit in cases of chyluria and fatty degeneration of the kidneys (*vide* p. 194).

CHAPTER VII.

TO DETERMINE THE CHEMICAL COMPOSITION OF A CALCULUS.

PULVERIZE the calculus, and heat to redness in a platinum crucible. The powder burns completely, and leaves hardly any residue (A).

The powder blackens, and leaves a considerable residue (B).

A. *The calculus is composed entirely of organic substances.*

The primitive calculus is saturated with nitric acid, and after evaporation is treated with ammonia (murexide reaction).

(a) Treated with caustic potash, nothing is evolved.	}	Uric acid.
(b) Treated with potash, ammonia is evolved.	}	Urate of ammonia.

The nitric solution, after evaporation with ammonia, gives the murexide reaction.	{	<p>(a) The nitric solution evaporated gives a yellow residue on cooling, which is coloured by potash (cold) reddish-yellow, and heated, violet-red.</p> <p>(b) The nitric solution evaporated gives a dark brown residue; the powder dissolves in ammonia and in potash; the ammoniacal solution, acidified by acetic acid, deposits microscopic hexagonal tubules; dissolved in potash, with the addition of nitro-prussiate of soda, a beautiful violet coloration is produced.</p>	}	<p>Xanthine.</p> <p>Cystine.</p>
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The powder burns with a brilliant flame.

{	(a) It is insoluble in potash. Treated with ether it gives a solution which on evaporation deposits pearly rhomboidal scales.	}	Cholesterine.
	(b) During the heating it evolves a burnt-horn odour; it is insoluble in potash, and precipitable by acetic acid.		

The powder treated with chloroform gives an orange-yellow colour, and on the addition of nitric acid gives the reaction of Gmelin.

{		}	Bile pigments.

B. The primitive powder, treated with nitric acid and ammonia, gives the murexide reaction; it contains urates with fixed base (soda, potash, magnesia, lime), oxalate of lime, phosphate of lime, carbonate of lime, ammonio-phosphate of magnesia.

(1) The residue is easily disintegrated by the blow-pipe. The primitive powder evolves ammonia on being treated with potash. Calcined alone, it gives off an ammoniacal odour.

It dissolves in acetic acid, and ammonia precipitates it from this solution in a crystalline form.

{		}	Ammonio-phosphate of magnesia.

(2) *The residue is unaffected by the blow-pipe.*

Non - alkaline residue.	{	(a) The residue is white. The powder does not effervesce either before or after calcination. It is soluble in hydrochloric acid, and is precipitated from this solution by ammonia. It also dissolves in acetic acid; the acetic solution gives, with oxalate of ammonium, a precipitate of oxalate of lime.	}	Basic phosphate of lime.

Alkaline residue.	{	(b) The primitive powder is unaffected by acetic acid; it is dissolved by mineral acids with effervescence, and is precipitated by ammonia. The alkaline residue effervesces with acids.	}	Oxalate of calcium.

{	(c) The powder, heated to white heat, develops an intense white flame; before calcination it effervesces with acids. It is precipitated from a neutralized chlorhydric solution.	}	Carbonate of lime.

(3) *The primitive powder gives with nitric acid and ammonia the uric acid reaction, but heated to redness it leaves a residue.*

Residue fusible by the blow-pipe.	(a) It communicates to the flame an intense yellow colour.	Urate of soda.
	(b) It imparts to the flame a violet colour, and chloride of platinum precipitates it from a chlorhydric solution.	
Residue non-fusible by the blow-pipe.	(a) After calcination its reactions are those of carbonate of lime.	Urate of lime.
	(b) It dissolves with feeble effervescence on being treated with dilute sulphuric acid, and is precipitated from this solution by phosphate of soda and ammonia.	
		Urate of magnesium.

In the case of a mixed calculus, with different layers superposed on one another, the following process is to be observed: Boil the calculus in a little distilled water; filter, and separately collect the filtered portion (A); wash the residue with boiling water. Boil the washed residue in dilute hydrochloric acid, and if effervescence result, the presence of *carbonate of lime* is indicated. Then filter the acid liquid. Collect the filtered liquor (B), and wash the residue, if any, with water.

Aqueous Solution (A).—The aqueous solution may contain urate of ammonium, urate of sodium, and urate of calcium. Evaporate a few drops of this solution on a watch-glass, and if but a small trace of residue be obtained, allow the remainder to repose, and regard the calculus as containing only an appreciable quantity of alkaline urates. If, on the contrary, an appreciable residue is obtained, boil about a fourth of the solution with a little caustic potash. Should the liquid contain ammonia, this gas is evolved, and may be recognised by its odour and other tests. The remainder of the solution is reduced by evaporation to a small volume, a little concentrated nitric acid is added, and evaporation to dryness is accomplished. A rose-coloured residue becoming red by the addition of ammonia indicates the presence of uric acid. The residue is incinerated and the ash dissolved

in water, the liquor being divided into two portions. Acidulate the one portion with acetic acid, and add a drop of oxalate of ammonia, which in presence of calcium produces a white precipitate. The other portion is acidulated with hydrochloric acid and evaporated to dryness. The presence of chloride of sodium is manifested by small cubical crystals.

Acid Solution (B).—This solution may contain chloride of sodium arising from the decomposition of carbonate or oxalate of calcium, of cystine, of phosphate of lime, or of ammonio-magnesium-phosphate. Add dilute ammonia so as to render the solution as neutral as possible without affecting its transparency, and then a little acetate of ammonium, which causes a *white precipitate* if the liquor contains *oxalate of lime* or *cystine*. The latter is rarely found in mixed calculi, and is easily separated from oxalate of lime by means of ammonia. If the acetate of ammonium precipitates, filter and add an excess of oxalate of ammonium to the filtered liquid; if the acetate of ammonium does not precipitate directly, treat the clear liquid with oxalate of ammonium without previous filtration. The presence of *calcium* is indicated by a white precipitate. If necessary, then filter and add ammonia in excess. The presence of *phosphoric acid* and *magnesium* is indicated by a *white precipitate*. If no precipitate is produced, add sulphate of magnesia. The presence of phosphoric acid is then indicated by the deposit of a white crystalline powder, after agitation of the liquid.

Residue (C).—This consists of *uric acid*, recognisable as above.

Sand and Gravel are analyzed like calculi. They should previously be submitted to microscopical examination, as they may present physical appearances by which they may be distinguished.

CHAPTER VIII.

MEDICAMENTS AND ACCIDENTAL ELEMENTS IN THE URINE.

Alcohol.	Mercury.
Antipyrine.	Naphthaline.
Antifebrine (Acetanilide).	Naphthol and other Phenols.
Arsenic and Antimony.	Bethol.
Alkaloids.	Phenacetine.
Aristol.	Salicylates.
Bromides.	Salol.
Carbolic Acid.	Saccharine.
Chloroform.	Strontium.
Chloral.	Tannin.
Chlorate of Potash.	Turpentine.
Iron.	Rhubarb.
Iodides.	Santonine.
Iodoform.	Thalline.
Kairine.	Urethan.
Lithia.	Filaments of Tissues;
Lead and Copper.	Grains of Starch.

Alcohol.—The greater portion of the alcohol taken into the system is changed by oxidation into carbonic acid and water, and consequently, when imbibed in large quantities, is found only in diminished quantity in the urine. This portion, however, may be separated from the urine by a process of distillation. About 100 c.c. of urine are to be distilled in a glass retort with a refrigerating apparatus. If to a few drops of the product of distillation a few drops of a dilute solution of bichromate of potash and dilute sulphuric are added, and heat applied, if the urine contain alcohol, the original yellow colour passes into green in consequence of the reduction of chromic acid to chromic oxide, while simultaneously an odour of aldehyde is

evolved. Otherwise (xanthogen reaction), the product of the distillation of the urine, once or twice rectified, is mixed with a little caustic potash and a few drops of sulphide of carbon; after agitation, an equal volume of water is to be added, and a drop of sulphate of copper solution. If any alcohol is present, a yellow precipitate of *xanthogenate of copper* forms.

The *reaction of Leben* may also be applied, as in the case of acetone (*vide* Acetone).

Antipyrine.—The frequent use of antipyrine renders its presence in the urine of clinical significance, and especially in its behaviour towards the usual albumen and sugar reagents.

Polarimetric Examination.—Feeble or concentrated solution of antipyrine does not affect the plane of polarization. It is otherwise with the antipyrine which has traversed the economy, and which has doubtless thus undergone some change; it deviates the plane of polarization to *the left*.

Nitric acid does not affect antipyrine, but Tanret's solution (*vide* Albumen, p. 126) gives a precipitate readily soluble in alcohol, and on being heated. The precipitate formed with peptones and alkaloids is even more soluble.

Esbach's reagent likewise precipitates antipyrine.

Mehu's reagent gives a precipitate of antipyrine very soluble in alcohol, and on application of heat, reappearing when the liquid cools.

Ferrocyanide of potassium and acetic acid solution is without effect on antipyrine. To be absolutely certain of the presence of albumen, five tests must be applied, thus:

	Rotatory Power.	Nitric Acid.	Tanret's Solution.	Esbach's Solution.	Mehu's Reaction.	Ferrocyanide of Potassium and Acetic Acid.
Albumen	—	Stable precip.	Stable precip.	Precip. stable	Precip. stable	Precip. stable
Antipyrine	—	0	Precip. soluble (a) by heat, (b) by alcohol	Precip. soluble (a) by heat, (b) by alcohol	Precip. soluble (a) by heat, (b) by alcohol	0
Alkaloids	0	0	Do.	Do.	Do.	0
Peptones	0	0	Do.	Do.	Do.	0

Having separated the albumen by heat, the presence of antipyrine may be demonstrated by means of perchloride of iron and Tanret's solution. The action of the perchloride of iron must not be confounded with the violet coloration due to the presence of salicylates in the urine (*vide* Salicylates, p. 237). Having proved the absence of salicylates, it may be concluded that the red coloration produced by the perchloride is due to antipyrine.

In this operation it is indispensable that the urine be not treated with subacetate of lead, as the presence of acetates occasions with the perchloride of iron the same colour as does antipyrine.

If the urine be decolorized by a 20 per cent. solution of nitrate of lead, and ferric chloride be added, a precipitate of chloride of lead is obtained.

Antipyrine causes a partial decoloration of Fehling's solution, the colour of the reagent passing from yellow to violet-gray. Antipyrine therefore interferes with Fehling's test in the presence of sugar. On treating urine containing antipyrine, and adding a few drops of fuming nitric acid, a green coloration is produced, which becomes red with an excess of the acid.

Antifebrine.—The presence of antifebrine is thus revealed: The urine is mixed with a fourth of its volume of concentrated sulphuric acid and boiled for a few minutes. On cooling, a few drops of carbolic acid or hypochlorite of lime are added. If antifebrine be present, the solution becomes red on the addition of nitric acid. Subsequently it becomes of a beautiful blue colour (iodophenol reaction). If the urine be agitated with chloroform, and evaporated, and the residue be heated with nitrate of mercury, a green coloration is the result, in which traces of acetanilide exist.

Arsenic and Antimony.—Destroy the organic matters with chlorate of potash and hydrochloric acid. Evaporate until the complete expulsion of the chlorine; wash the residue with water; evaporate the filtered liquid to a third of its volume, and test for the metals by Marsh's method.

Alkaloids.—The animal alkaloids found in the urine are of two varieties, viz.: (1) The ptomaines, which develop in dead

matter on putrefaction; (2) the leucomaines, which are excreted during life. These alkaloids are distinguished from alkaloids of vegetable origin by the Brouardel-Boutiny reaction (ferrocyanide of potassium and perchloride of iron). Vegetable alkaloids have no effect on this reagent, while leucomaines on contact with it cause an intense blue coloration, morphia alone giving an intense reaction, and atropia a feeble one.

The solution of Von Jaksch—

Potass. Iod.	10 grammes
Iodine	5 ,,
Water	10 ,,

—gives a green fluorescence on contact with leucomaines.

Vegetable Alkaloids.—Tanret's solution forms the most delicate test for vegetable alkaloids. It gives a white precipitate, which disappears on the application of heat or the addition of alcohol.

Trichloroacetic Acid, which is sometimes employed as an albumen reagent, precipitates alkaloids when concentrated. This precipitate is dissolved by the addition of water, by heat, by the addition of alcohol, and by an excess of the reagent.

The frequent administration of quinine as a therapeutic agent renders its presence in the urine important. When the residue of the evaporation with ether is treated with a drop of sulphuric acid, a marked blue fluorescence is an excellent test of quinine. The acid liquid gives the following further characteristic reactions of quinine: Chlorinated water and ammonia, a green colour; chlorinated water with one drop of a solution of ferrocyanide of potassium and ammonia, a red colour.

Instead of chlorinated water, which is very unstable, the liquor of Labarraque may be employed.

Aristol is eliminated in the urine under the form of an alkaline iodide and of thymol. Its presence must be demonstrated by the tests employed for these agents.

Bromides.—The action of chlorides on bromides being frequently obscured by organic matters, the following process recommended by M. Bruneau should be followed. Heat gently

in a test-tube, and agitate. Chlorine gas is given off. To the aqueous solution add a little chloroform or sulphide of carbon; agitate, and allow to repose. Bromine is indicated by the chloroform which rests below the urine assuming a deep reddish-yellow colour, which disappears on agitation with potash or soda.

Carbolic Acid appears in the urine after the internal administration of this drug in the form of phenyl-sulphate of potash. To demonstrate its presence, add a little hydrochloric acid to the urine and distil. To the distillate add bromine water, when a precipitate of tribromophenol is obtained. With perchloride of iron a blue coloration is produced. With Millon's reaction a red colour is obtained. A drop of aniline and a few c.c. of the liquor of Labarraque give a blue coloration, which appears slowly, but which lasts many weeks.

Chloroform.—As the presence of chloroform in urine is a contested point, its mode of detection need not be described.

Chloral.—Chloral is not naturally eliminated, nor in the form of chloroform. Its ultimate products are carbonic acid and urochloralic acid. The latter reduces Fehling's solution.

Chlorate of Potash.—This salt is entirely eliminated by the urine. To demonstrate its presence, add to the urine a few drops of sulphate of indigo, dilute sulphuric acid, and a solution of sulphate of soda. The blue colour instantly disappears in presence of chlorate of potash.

Iron.—The presence of iron is easily demonstrated in the urine. Add a few drops of nitric acid, and boil. Peroxide of iron is thus produced. Add a solution of ferrocyanide of potassium, when the characteristic coloration of Prussian blue appears.

Iodides.—Iodides pass rapidly into the urine. To demonstrate their presence, add a few grains of starch. Agitate with freshly-prepared chlorine water, or one or two drops of fuming nitric acid. The iodine thus set free assumes a beautiful characteristic blue colour. An excess of nitric acid must be avoided. In place of nitric acid or chlorinated water, an alkaline hypochlorite, or perchloride of iron may be employed.

Test for Iodine in Urine (Journal de Médecine de Paris, September 23, 1888).—To 10 c.c. of urine add 2 c.c. of dilute

sulphuric acid (one part to five of water) ; then add five drops of solution of starch freshly prepared. To this mixture add, drop by drop, a 1 per cent. solution of nitrate of potash, shaking the vessel. If the urine contain iodine, the addition of the first few drops will produce a violet or more or less intense blue coloration, which will disappear on the addition of a drop of 10 per cent. solution of hyposulphite of soda. The addition to the urine of a few drops of sulphuret of carbon intensifies the reaction.

Iodoform may be found in the urine after the administration of this drug. Agitate the urine with ether ; spontaneous evaporation leaves iodoform as a residue. It is characterized by its odour, and, microscopically, by its hexagonal scales.

Kairine.—A drop of perchloride of iron solution gives, with kairine, a violet colour, which rapidly turns into brown. Bichromate of potash gives a violet pigment which, with alcohol, gives a mauve solution. The addition, drop by drop, of a 10 per cent. solution of chloride of lime to urine acidified by acetic acid, and containing kairine, gives a fuchsine colour.

Lithia.—Calcine completely a certain quantity of urine so as to obtain a white ash, which dissolve in dilute hydrochloric acid. Filter the liquid, evaporate to dryness, and dissolve in equal parts of ether and absolute alcohol. Evaporate the alcoholic liquor to dryness, and test the residue with the blow-pipe. If it contain lithia, a red flame is the result. Spectroscopic examination reveals characteristic rays.

Lead and Copper.—Evaporate the urine to dryness, and carbonize the residue at as low a temperature as possible. Ignite in a porcelain capsule, and moisten from time to time with concentrated nitric acid. On cooling treat the ash with water acidulated with a few drops of nitric acid, filter, and test the filtrate for lead and copper. With lead sulphuretted hydrogen gives a black or dark-brown precipitate, sulphuric acid a white precipitate, and chromate of potash a yellow precipitate. If the urine contain copper it presents a bluish colour, if the quantity is not extremely feeble ; with sulphuretted hydrogen a black or brown colour results ; ammonia gives a greenish-blue precipitate, which dissolves in an excess of the reagent, giving an azure blue

colour; and ferrocyanide of potassium gives a brown or reddish-brown colour.

Mercury.—Acidulate the urine with hydrochloric acid, and add powdered zinc, which precipitates all the mercury. Wash the precipitate with hot water, then with alcohol and ether, and treat after Ludwig's method. Secondly, acidulate the urine with hydrochloric acid and heat. Cool, and heat anew. Plunge into the liquid several times a thin metallic plate composed of copper and zinc, on which the mercury deposits. Wash the plate, and expose to iodine vapour, when iodide and biniodide of mercury are formed; or treat the plate after Marsh's method.

Naphthaline.—If to urine containing naphthaline a few drops of ammonia be added, or soda, a beautiful blue colour results. When naphthaline is administered as a drug the urine becomes of a characteristically dark colour.

Naphthol and other Phenols.—Treat a given quantity of urine with half its volume of chloroform, agitate gently, and pour into a decantation apparatus. The decanted chloroform is received in a test-tube, and a pastil of caustic potash is added. Characteristic coloured spots result, varying with the nature of the phenol (Desquelle, *Répertoire de Pharmacie*, 1890, p. 101).

With ordinary phenol, a rose colour.

With thymol, a deep violet colour.

With resorcine, a rose colour.

With hydroquinon, a golden yellow colour.

With naphthol (x), a sky-blue colour.

With naphthol (b), a greenish-blue.

With pyrogallol, a violet colour.

With creosote, a violet colour.

With guaiacol, a rose-violet colour.

Yvon commends the subjoined as naphthol tests:

- | | | | | |
|---|-----|-----|-----|------------|
| (i.) Acid nitrate of mercury | ... | ... | ... | 5 grammes. |
| Nitric acid | ... | ... | ... | 15 „ |
| (ii.) Saturated solution of nitrate of potash | ... | ... | ... | 10 „ |
| Sulphuric acid | ... | ... | ... | 5 „ |

These two tests give with naphthol a red colour.

Bethol, or Salicylate of Naphthol.—Bethol is eliminated in the urine as naphthol, and salicylic and salicyluric acids.

Grenouillet (*Répertoire de Pharmacie*, 1890, p. 470) recommends the following process for its isolation: Reduce 500 c.c. of urine to the volume of 150 c.c.; after cooling, filter, and agitate the liquid with its volume of ether. Evaporate, and dissolve the residue in boiling water. After cooling, salicylic acid is revealed by perchloride of iron (*vide* Salicylates).

Otherwise add to the urine 2 per cent. of sulphuric acid and distil. Agitate the distilled product with chloroform. This liquor gives with caustic potash the characteristic blue colour of naphthol.

Phenacetine.—Strongly acidulate the urine with hydrochloric acid, and heat. On cooling add from one to two drops of a perchloride of iron solution, when a reddish-brown coloration is produced. Or to 2 c.c. of urine of an acid reaction add from four to five drops of a solution of chromic acid (3 per cent.). At the point of contact of the two fluids a brown coloration appears.

Salicylates.—A few drops of a solution of perchloride of iron cause a violet coloration in urine containing a salicylate; but if the salicylate exist in feeble proportion, and the urine contain a large proportion of phosphates, a precipitate of phosphate of iron forms, which obscures the salicylate reaction. In this case the salicylic acid must be isolated. To accomplish this, add to 100 c.c. of urine from six to eight drops of hydrochloric acid, and agitate gently with 6 c.c. of ether. After sufficient repose the ether is decanted and poured out on a saucer containing a few drops of a 10 per cent. solution of perchloride of iron. After evaporation of the ether a beautiful violet coloration ensues.

Salol, or salicylate of phenol, is not normally voided with the urine. The derivatives of salol reduce Fehling's solution, and deviate the plane of polarization to the left. To distinguish glucose in presence of salol, the urine decolourized by a tenth part of its volume of subacetate of lead is placed in a tube with 5 centigrammes of hydrochlorate of phenylhydrazine and 0.20 of pure soda. The liquid becomes of a yellow colour, and is heated for half an hour on a water-bath. It is then poured into

a suitable glass vessel and cooled, when, if it contain sugar, a crystalline deposit results, recognisable by the microscope. With salol the deposit is amorphous.

Saccharine.—Agitate the urine with a few drops of sulphuric acid, and then with a mixture of ethylic and petrolic ether. Evaporate the ethereal liquid, and dissolve the residue in a little hot water. The solution possesses a sugary sweetness most marked in the case of saccharine. Neutralize the residue with carbonate of soda, and treat with a small excess of nitrate of mercury. A saccharinate of mercury results, which may after washing be collected and dried on a filter. Place this in a test-tube, and add twice its volume of resorcline. Add a few drops of sulphuric acid, and heat. Divers colours result, the mass becomes resinous, and gives off sulphurous acid. Allow the remainder to cool, dilute with water, and saturate with potash or caustic soda. There results a reddish-brown liquid with green fluorescence. This fluorescence becomes manifest if a few drops of the liquid be added to a tube containing water.

Strontium.—The urine concentrated to a tenth of its volume is filtered after cooling. To a portion of it which is perfectly limpid, a few drops of neutral chromate of potash solution are added. If there be no result, it may be inferred that no salts of barium are present. To another perfectly limpid portion of urine a few drops of sulphuric are added. A precipitate of sulphate of strontium is formed. Ignite with carbon, and a transformation into sulphide takes place. Dissolve the residue in hydrochloric acid, and examine for strontium spectroscopically.

Tannin.—Tannin is eliminated in the urine in the form of gallic acid. With perchloride of iron, gallic acid in urine gives a black-blue precipitate. Alkalies give a brown and black colour.

Turpentine with protochloride of antimony gives a red colour; and M. Loison (*Rép. de Pharm.*, 1890) recommends the following test process: Evaporate 500 c.c. of urine on a water-bath to the consistence of an extract. To the residue add 10 c.c. of boiling alcohol, filter, and reduce by evaporation to 5 c.c. Add to these 5 c.c. a few drops of hydrochloric acid, and place

in a fine tube containing some crystals of protochloride of antimony. Gently heat the tube, and after a minute's boiling, if the urine contain turpentine, an intense red colour appears.

Rhubarb.—After partaking of rhubarb, a deep yellow colour is imparted to the urine, sometimes resembling the urine of jaundice. The addition of an alkali to such urine causes a red colour. The following reactions distinguish rhubarb from santonine: In the case of rhubarb, senna, etc., the coloration produced by the alkali persists for more than twenty-four hours. The coloration appears promptly with soda or ammonia. Reducing agents, such as powder of zinc and sodium, cause the colour to disappear. Baryta solution and lime-water precipitate the colouring matter.

Santonine.—The coloration caused by alkalies does not persist beyond twenty-four hours, and is slow to appear. Reducing agents do not cause the colour to disappear. Baryta and lime-water do not precipitate the pigment, and the liquid becomes limpid on repose, but the red colour persists.

If the urine be acidified with sulphuric acid and agitated with amyl alcohol, no coloration results in the case of santonine, while in the presence of rhubarb a yellow colour is the result.

Thalline.—Urine containing thalline exhibits a brownish tint with greenish reflection. To identify its presence, treat the urine with chloroform or with ether, decant, and evaporate in a porcelain crucible, when contact with perchloride of iron will give a beautiful green colour.

Urethan.—Agitate 500 c.c. of urine with a sufficient quantity of ether. Decant, wash with distilled water, and completely evaporate. Add to from 10 to 20 c.c. an excess of potash. To this add a solution of perchloride of mercury, when a more or less abundant white precipitate is obtained.

Filaments of Tissues ; Grains of Starch.—These bodies are easily recognised by their chemical and microscopic characters. Cotton fibres are coloured blue by iodine and sulphuric acid. Starch gives a characteristic blue colour with a solution of iodine.

APPENDIX.

CONVERSION OF GRAMMES INTO GRAINS AND VICE VERSÀ.

<i>Grammes to Grains.</i>	<i>Grains to Grammes and Milligrammes.</i>
1 = 15·43235	1 = 0·6480 or 64·80
2 = 30·86470	2 = 0·12958 „ 129·58
3 = 46·29705	3 = 0·19437 „ 194·37
4 = 61·72940	4 = 0·25916 „ 259·16
5 = 77·16175	5 = 0·32395 „ 323·95
6 = 92·59410	6 = 0·38874 „ 388·74
7 = 108·02645	7 = 0·45353 „ 453·53
8 = 123·45880	8 = 0·51832 „ 518·32
9 = 138·89115	9 = 0·58311 „ 583·11

COMPARISON OF MEASURES (ENGLISH INTO METRIC).

1 minim	= 0·5916 c.c.
1 fluid drachm	= 3·5495 c.c.
1 fluid ounce	= 28·396 c.c.
1 pint	= 567·92 c.c. = 0·56792 litre.
1 quart	= 1·3584 litre.
1 cubic inch	= 16·386 c.c.

COMPARISON OF WEIGHTS (METRIC INTO ENGLISH).

1 milligramme	= 0·01543 grain (=nearly the $\frac{1}{65}$ th)
1 centigramme	= 0·15432 grain
1 decigramme	= 1·54323 grains
1 kilogramme	= 35·27395 ounces (Avoirdupois)
	or 2·2046213 lbs. (Avoirdupois)

To convert grammes per litre into grains per gallon, multiply by 70.

To convert grains per gallon into grammes per litre, multiply by 0.014286.

To convert grammes per fluid drachm into grains per fluid ounce, multiply by 123.46.

1 millimetre = 0.03937 inch

25.4 mm. = 1 inch

Johnson's 'Analyst's Laboratory Companion.'

To convert degrees of *Fahrenheit's* thermometer into those of the *Centigrade* scale, subtract 32 and multiply by $\frac{5}{9}$; and conversely to convert *Centigrade* readings to *Fahrenheit* scale, multiply by $\frac{9}{5}$ and add 32.

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 ERRATA.

- Page 38, line 15, *for* 'he observed' *read* 'Bonchard observed,' etc.
 „ 145, „ 1, *for* 'Zöhär' *read* 'Zähör.'
 „ 165, second line from bottom of page, *for* 'Böttiger' *read* 'Böttger.'
 „ 213, „ „ „ *for* 'Ascaridis' *read* 'Ascaris.'
 „ 214, line 8, *for* 'Bacillus urinæ' *read* 'Bacillus urææ.'

THE END.

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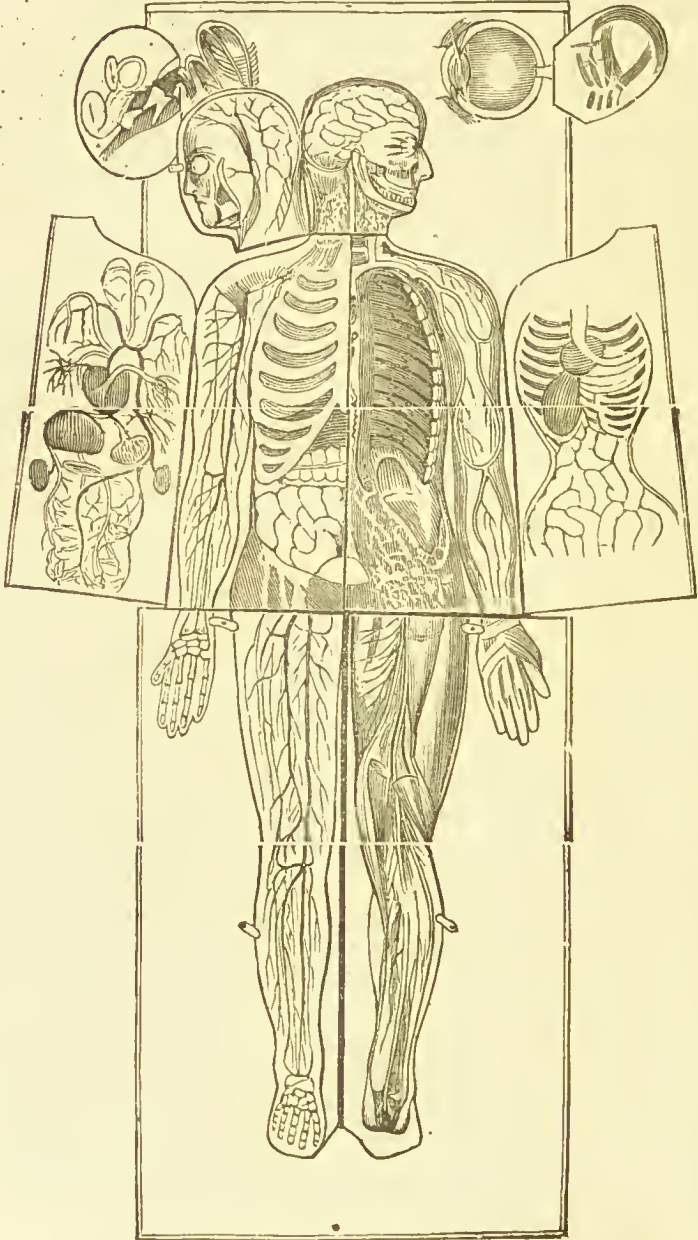
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